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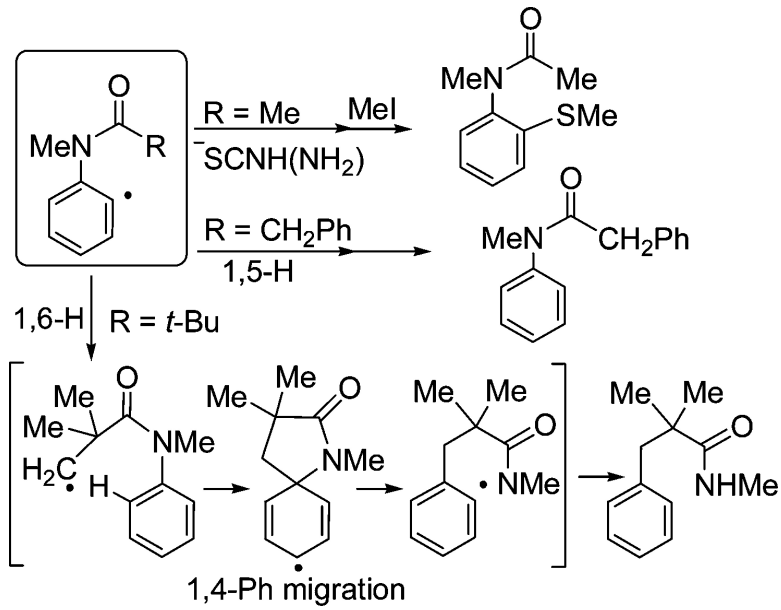

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Competitive Reaction Pathways for *o*-Anilide Aryl Radicals: 1,5- or 1,6-Hydrogen Transfer versus Nucleophilic Coupling Reactions. A Novel Rearrangement to Afford an Amidyl Radical

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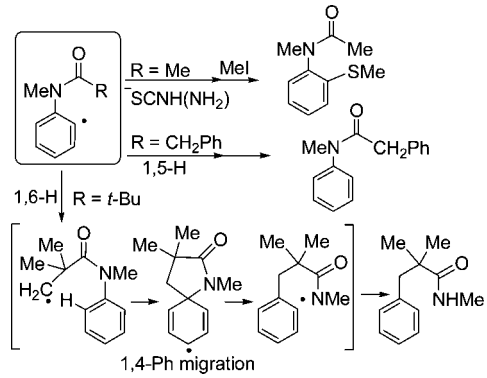

The photoinduced reactions of *o*-iodoanilides (*o*-IC$_6$H$_4$N(Me)COR, **4a**−**d**) with sulfur nucleophiles such as thiourea anion (**1**, $^-$SCNH(NH$_2$)), thioacetate anion (**2**, MeCOS$^-$), and sulfide anion (**3**, S^{2-}) follow different reaction channels, giving the sulfides by a radical nucleophilic substitution or the dehalogenated products by hydrogen atom transfer pathways. After an initial photoinduced electron transfer (PET) from **1** to iodide **4**, the *o*-amide aryl radicals **12** are generated. These aryl radicals **12** afford alternative reaction pathways depending on the structure of the α-carbonyl moiety: (a) **12b** (R = Me) adds to **1** to render the methylthio-substituted compounds by quenching the thiolate anion intermediate with MeI after irradiation; (b) **12c** (R = −CH$_2$Ph) follows a 1,5-hydrogen transfer to give a stabilized α-carbonyl radical (**17**); and (c) **12d** (R = *t*-Bu) affords 1,6-hydrogen transfer, followed by a 1,4-aryl migration to render an amidyl radical (**20**), which is reduced to the *N*-benzyl-*N*,2-dimethylpropanamide (**10**). Together with this last rearranged product, the ipso substitution derivative was also observed. Similar results were obtained in the PET reactions of **4d** (R = *t*-Bu) with anions **2** and **3** under *entrainment* conditions with the enolate anion from cyclohexenone (**5**) or the *tert*-butoxide anion (**6**). From this novel rearrangement, and only under reductive conditions by PET reaction with anion **5**, iodide **4d** (R = *t*-Bu) affords quantitatively the propanamide **10**. The energetic of the intramolecular rearrangements followed by radicals **12b**−**d** were rationalized by B3LYP/6-31+G* calculations.

Introduction

At present, the use of radical reactions for the synthesis of target organic compounds is widely recognized, and many studies describe the synthetic applications of different radical procedures.[1] The radical nucleophilic substitution involving electron transfer (ET) steps or the S$_{RN}$1 mechanism has proven to be a versatile mechanism for replacing an adequate leaving group at the ipso position by a nucleophile. This process is considerably broad in scope in relation to substrates and nucleophiles and to synthetic capabilities.[2] Carbanions, nitrogen nucleophiles, and anions from tin, phosphorus, arsenic, antimony, sulfur, selenium, and tellurium are able

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(1) (a) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001. (b) *Top. Curr. Chem.* **2006**, *263* and *264*. Rossi, R. A.; Peñéñory, A. B. *Curr. Org. Synth.* **2006**, *3*, 121–158.

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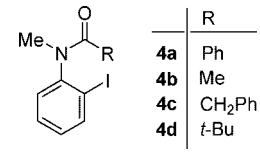
to react with nonactivated aryl halides to yield new C−C or C−heteroatom bonds.[2]

Among the sulfur-centered nucleophiles known to react under photostimulation we can find alkane, arene, and heteroarene thiolate anions. Recently, we have described the reactivity of sulfur anions, such as thiourea anion (**1**, $^{-}SCNH(NH_2)$),[3] and thioacetate anion (**2**, $MeCOS^{-}$)[4] in photoinduced aromatic radical nucleophilic substitution as a "one-pot" method for the synthesis of several sulfur aromatic compounds in moderate to good yields. These reactions offer a very good alternative to introduce sulfur functionalities in aryl compounds at the position of the halide leaving group. By using hydrogen abstraction from DMSO as a competitive reaction, we have also determined the absolute rate constants for the addition of ions S^{2-} (**3**), **1**, **2**, thiobenzoate ($PhCOS^{-}$), and benzene thiolate (PhS^{-}) anions to 1-naphthyl radicals (0.5×10^9 M^{-1} s^{-1}, 1.0×10^9 M^{-1} s^{-1}, 1.2×10^9 M^{-1} s^{-1}, 3.5×10^9 M^{-1} s^{-1}, and 5.1×10^9 M^{-1} s^{-1}, respectively, at 25 °C).[5] Furthermore, for the reactions of 1-bromonaphthalene with anions **1**, **2**, and $PhCOS^{-}$, we have elucidated the mechanism for the photoinduced electron transfer (PET) at the initiation step, the chain length, as well as the nature of the chain carrier in the propagation cycle.[5b]

It is known that the *o*-iodoanilides with hydrogen atom at the α-carbon are appropriate substrates for the synthesis of oxindoles derivatives by intramolecular radical nucleophilic substitution reactions.[6] In addition, the *o*-haloanilides are also suitable precursors of aryl radicals employed for the generation of radicals adjacent to a carboxyl group by a 1,5-hydrogen transfer. The so-formed radicals can follow synthetically useful reactions, such as intramolecular cyclization,[7] intermolecular addition,[7b] or homolytic substitution to afford oxindoles.[8]

Taking into consideration our simple and effective methodology for replacing an iodide atom by a sulfur anion, we are concerned with finding out the scope of this reaction for the synthesis of sulfur heterocycles. Thus, we have studied the reactivity of *o*-iodoanilides with anions **1**−**3** in photoinduced reactions in DMSO. Replacing the iodide by a sulfur anion and its subsequent reaction with the carbonyl group would render benzothiazole derivatives. Therefore, and in mechanistic terms, it is of interest to study the effect of the nature of the α-carbonyl alkyl moiety on the reactivity of the *o*-iodoanilides in photoinduced reactions with sulfur anions. For this purpose, *N*-methylanilides **4a**−**d** were chosen,[9] for which the R group comprises Ph, Me, $PhCH_2$, and *t*-Bu, well suited for the mechanistic elucidation of possible competitive reaction channels (Chart 1).

CHART 1



	R
4a	Ph
4b	Me
4c	CH_2Ph
4d	*t*-Bu

Results

o-Iodoanilides **4** were synthesized from *o*-iodoaniline by standard acylation and alkylation procedures. These anilides are found predominantly in the *E* conformation (CO/Ar trans >%95).[7b] Table 1 summarizes the results obtained in the photoinduced reactions of thiourea anion **1** with anilides **4a**−**c** and after being quenched with MeI.

Iodide **4a** (R = Ph) did not react with anion **1** after 3 h of irradiation, and the substrate was completely recovered. Similar results were found with other sulfur anions (**2** and **3**) and with suitable electron donors, such as enolate anion of cyclohexenone (**5**) or *tert*-butoxide anion (**6**) commonly used as *entrainment*[10] reagents in radical nucleophilic substitutions. Both alkoxide anions are able to transfer one electron to aryl iodides under irradiation to initiate an $S_{RN}1$ reaction; however, they are not reactive toward aryl radicals in the addition step.[4]

TABLE 1. Reactions of *o*-Iodoanilide with Thiourea Anion in DMSO[a]

			product yield[c]		
entry	**4** (ArI), R	compound added[b]	convn	ArSMe (**7**)	ArH (**8**)
1	**4a**, Ph				
2[d]	**4b**, Me		<4		
3			100	93	5
4		*p*-DNB	58	43	<5
5[e]			100	97	<5
6[d]	**4c**, CH_2Ph				
7			65		45
8		*p*-DNB	18		23
9		TEMPO	20		32
10[f]			100		<4[g]
11[h]			67		50[i]

[a] ArI = **4a**−**c**, 0.05 M; anion **1**, 0.5 M (ratio **4**:**1** = 1:10). After 3 h of irradiation under nitrogen atmosphere, the reaction was quenched by MeI. [b] Compounds added (20%). [c] Determined by GC using the internal standard method, error 5%. The conversion (convn) was determined by quantification of the recovered substrate. [d] In the dark. [e] ArI = 0.1 M. [f] In the absence of anion **1**, with an ArI/*tert*-butoxide ion ratio of 1:10. [g] Together with oxindole **9** in 95% yield. [h] In the absence of anion **1**, with an ArI/enolate anion of cyclohexenone ratio of 1:1. [i] Together with oxindole **9** in 23% yield.

For the methyl derivative **4b** (R = Me), there was no reaction with anion **1** after 3 h in the dark. Under photostimulation (λ_{max} = 365 nm), however, it gave mainly *N*-methyl-*N*-(2-methylthio)phenyl)acetamide (**7b**) (93%) and a small amount of *N*-methyl-*N*-phenylacetamide (**8b**) (5%), after quenching with MeI

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(3) Argüello, J. E.; Schmidt, L. C.; Peñéñory, A. B. *Org. Lett.* **2003**, *5*, 4133–4136.

(4) Schmidt, L. C.; Rey, V.; Peñéñory, A. B. *Eur. J. Org. Chem.* **2006**, 2210–02214.

(5) (a) Argüello, J. E.; Schmidt, L. C.; Peñéñory, A. B. *ARKIVOC* **2003**, *Part 5* (x), 411–419. (b) Schmidt, L. C.; Argüello, J. E.; Peñéñory, A. B. *J. Org. Chem.* **2007**, *72*, 2936–2944.

(6) (a) Wolfe, J. F.; Sleevi, M. C.; Goehring, R. R. *J. Am. Chem. Soc.* **1980**, *102*, 3646–3647. (b) Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435–443.

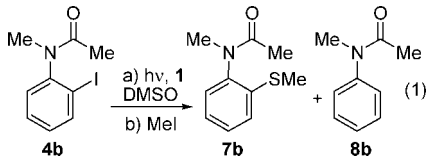
(7) (a) Jones, K.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1992**, 1766–1767. (b) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343–7366. (c) Xu, X.; Che, X.; Gao, S.; Wu, J.; Bai, X. *Synlett* **2005**, 1865–1868.

(8) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977–978.

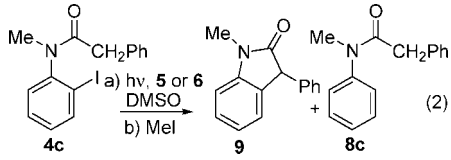
(9) Preliminary results showed that when a solution of *o*-iodophenylacetamide and thiourea anion in a 1:10 ratio, respectively, was irradiated for 3 h, and after addition of MeI, the substrate was recovered methylated on the nitrogen atom. Thus, deprotonation of the nitrogen inhibited the photoinduced initiation reaction. In view of this result, we performed the present study with *N*-methyl derivatives.

(10) Braslavsky, S. E. *Pure Appl. Chem.* **2007**, *79*, 293–465.

(eq 1). This photoinduced reaction was strongly inhibited by the addition of 20% of *p*-dinitrobenzene (*p*-DNB), a good electron acceptor. Moreover, when the concentration of iodide doubled, the photoinduced reaction afforded quantitatively product **7** (Table 1, entries 1−5).



Anilide **4c** (R = CH_2Ph) did not react with anion **1** in the dark, and after 3 h, the photoinduced reaction afforded the reduction product (**8c**) in 45% isolated yield without any traces of a substitution product from the thiourea anion. Unfortunately, when this last reaction was performed in DMSO-d_6 as solvent, product **8c** was not labeled by deuterium; this was because in the basic reaction medium the benzylic hydrogens are easily exchanged during workup. This photostimulated reaction was inhibited by the presence of *p*-DNB or TEMPO (Table 1, entries 6−9). When the photoinduced reaction was performed in the absence of thiourea anion with a 10-fold excess of anion **6**, oxindole **9** was obtained in 95% isolated yield, together with traces of **8c** (eq 2). On the other hand, the photostimulated reaction of aryl iodide **4c** with anion **5** in a molar ratio 1:1 gave the reduction product **8c** and **9** in 50% and 23% yield, respectively (Table 1, entries 10 and 11).

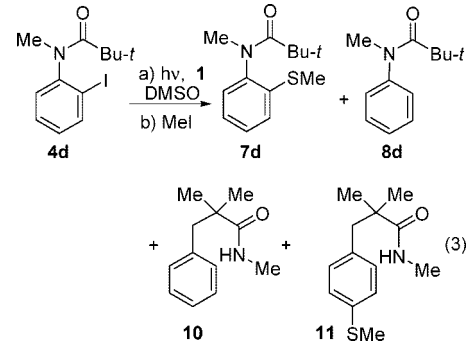


Finally, the reactivity of *tert*-butyl derivative **4d** was studied under different reaction conditions; the results are summarized in Table 2. The reaction of iodide **4d** with thiourea anion (**1**) gives, after 3 h of irradiation and the addition of MeI, the expected methylthio derivative **7d** from ipso substitution in only 10% yield and the dehalogenated product **8d** in 2% yield. Apart from these derivatives, two main products are observed: a reduction (**10**) and a substitution (**11**) derivative in 38% and 25% yields, respectively, both arising from a radical rearrangement (Table 2, entry 1, eq 3).

TABLE 2. Reactions of *o*-Haloanilide (R = *t*-Bu, 4d) with Nucleophiles in DMSO[a]

		product yield[b]				
entry	Nu^-	convn	**7d**	**8d**	**10**	**11**
1	**1**	97	10	2	38	25
2[c]	**1**	70	6		13	15
3[d]	**1**	<4				
4[e]		100			70[f]	
5[e]	**2**	70	10	3	20	12
6[e]	**3**	86	5	5	2	15

[a] ArI = **4d**, 0.05 M; nucleophiles (Nu^-), 0.5 M, (ratio **4d**/Nu^-, = 1:10). After 3 h of irradiation under nitrogen atmosphere, the reaction was quenched by MeI. [b] Determined by GC using the internal standard method, error 5%. The conversion (convn) was determined by quantification of the recovered substrate. [c] In the presence of 20 mol % of TEMPO. [d] In the dark. [e] In the presence of the enolate anion of cyclohexenone, 0.25 M. [f] Isolated.



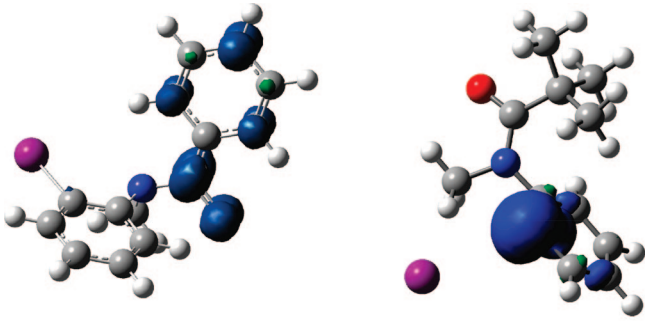
In the presence of 20 mol % of a highly efficient radical trap like TEMPO, this photoinduced reaction was strongly inhibited with only a 30% conversion yield. Moreover, this reaction did not occur in the dark, and the substrate was recovered in 96% yield. When pivalamide **4d** was irradiated in the presence of anion **5**, a good electron donor, and in the absence of thiourea anion, only the rearranged reduction product **10** was isolated in 70% yield. In addition, when this last reaction was performed in DMSO-d_6 as solvent, the reduced rearranged product **10** was not labeled by deuterium (Table 2, entries 2−4).

The reactivity of this pivalamide **4d** toward thioacetate (**2**) and sulfide (**3**) anions was determined under *entrainment* conditions in the presence of anion **5** or **6**. Although the photoinduced reactions of these sulfur anions proceeded at low conversion rates, the same products with a distribution similar to that of the reaction with thiourea anion were observed (Table 2, entries 5 and 6).

Discussion

A detailed study of the photochemical reactions between *o*-iodoanilides **4** with different sulfur-centered nucleophiles was performed in DMSO. The absence of reaction in the dark, the inhibition of the photoinduced reactions in the presence of an electron acceptor such as *p*-DNB or by a radical trap like TEMPO, the formation of the dehalogenated products **8**, and the rearranged derivatives **10** and **11** (Tables 1 and 2) evidence, in these reactions, the participation of aryl radicals. These intermediates are generated by a PET reaction from a suitable electron donor to aryl iodide **4**. Electron transfer to these compounds may follow either a concerted dissociative pathway through which the electron capture is accompanied by the dissociation of the C−iodine bond or a stepwise mechanism with formation of radical anions intermediates. Theoretical inspection of the anionic surface of **4a**−**d** with the B3LYP functional and the LANL2DZ basis set in the presence of DMSO, simulated as a continuum, shows the ET to **4b**−**d** to be dissociative; in other words, no radical anion intermediates could be located on these surfaces; the ET to these compounds leading to the dissociated radicals (**12b**−**d**)−halide anion fragments (Scheme 1 and Figure 1b). On the other hand, the ET to **4a** follows a stepwise pathway with formation of a π radical anion $\mathbf{4a}^{\bullet-}$ in which the unpaired electron mainly localizes at the PhCO moiety (Figure 1a).

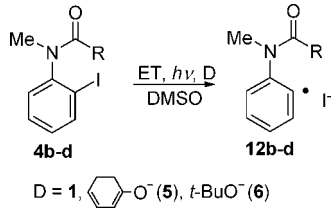
As shown in Figure 1a, the unpaired spin density in $\mathbf{4a}^{\bullet-}$ is highly localized at the PhCO moiety. On the basis of this spin density distribution, the dissociation of $\mathbf{4a}^{\bullet-}$ by an intramolecular ET from the π PhCO system to the σ^* C−iodine bond is expected to be a disfavored process.[11] In agreement with this finding, **4a** was found to be unreactive under our experimental



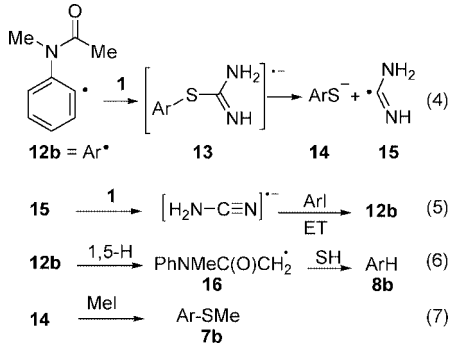
(a) (b)

FIGURE 1. B3LYP/LANL2DZ unpaired spin density of (a) $\mathbf{4a}^{\bullet-}$ and (b) of the charge-radical complex formed by ET to **4d**, both in DMSO (density isovalue = 0.005).

SCHEME 1



SCHEME 2

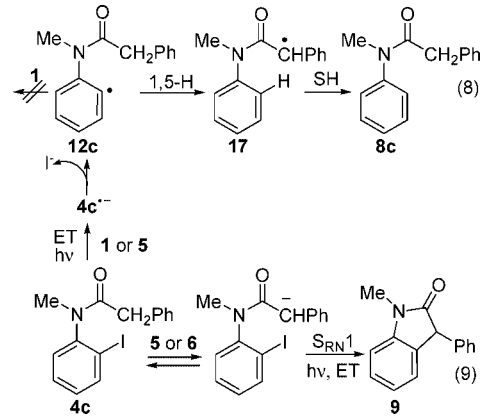


conditions. Similar results have been reported for the reaction of *o*-iodohalobenzenes with enolate anions of aromatic ketones in DMSO under ET conditions. In this system, the formation of monosubstitution with halide retention as main reaction product was rationalized by theoretical studies and attributed to the intermediacy of a highly stabilized radical anion having the unpaired spin at the π ArCO system.[12]

As seen from Tables 1 and 2, aryl radicals **12b**−**d** follow different reaction pathways as a function of the structure of the α-carbonyl alkyl moiety (R).

Aryl iodide **4b** gave methylthio derivative **7b** in excellent yields, and the observed results (Table 1, entries 2−5) can be described by a radical nucleophilic substitution mechanism, such as the following: aryl radical **12b** (R = Me, Scheme 2) adds efficiently to thiourea anion to afford a new radical anion intermediate **13**, which fragments into arene thiolate ion **14** and

SCHEME 3



carbon radical **15** (eq 4, Scheme 2). Deprotonation of carbon radical **15** renders cyanamide radical anion which, by ET to the aryl iodide, may continue the $S_{RN}1$ cycle (eq 5, Scheme 2).[5b] The reduction or dehalogenation product **8b** can be ascribed to a competitive 1,5-hydrogen atom transfer to render an α-carbonyl methyl radical (**16**) followed by subsequent hydrogen atom abstraction from the solvent (eq 6, Scheme 2). After irradiation, thiolate ion **14** is quenched with MeI to give methylthio derivative **7b** (eq 7, Scheme 2). Due to steric hindrance, the addition of anion **14** to the *o*-amidophenyl radical **12b** is not a competitive reaction and Ar_2S is not formed.[4]

The photoinduced reaction of iodide **4c** with anion **1** gave the dehalogenation product **8c**, and no trace of the coupling product was observed. In this reaction, the aryl radical intermediate **12c** (R = CH_2Ph, Scheme 3) yields, by 1,5-hydrogen transfer, an α-carbonyl radical stabilized by the phenyl group (**17**). This reaction is faster than the coupling of aryl radical intermediate **12c** with thiourea anion.[13] As a result, radical **17** affords **8c** as the only product by hydrogen atom abstraction from the solvent (eq 8, Scheme 3). In the absence of thiourea anion, and with an excess of potassium *tert*-butoxide, the deprotonation of the α-carbonyl carbon is complete and the resulting enolate anion affords oxindole **9** (95% yield) by an intramolecular $S_{RN}1$ reaction (eq 9, Scheme 3). A similar ring-closure reaction with a 64% yield was reported using the strong base lithium diisopropylamide in tetrahydrofuran at −78 °C.[6] In the presence of only 1 equiv of the enolate anion of cyclohexenone, the deprotonation equilibrium is not completely favorable to the generation of the enolate anion, and both **8c** and **9** products were observed.

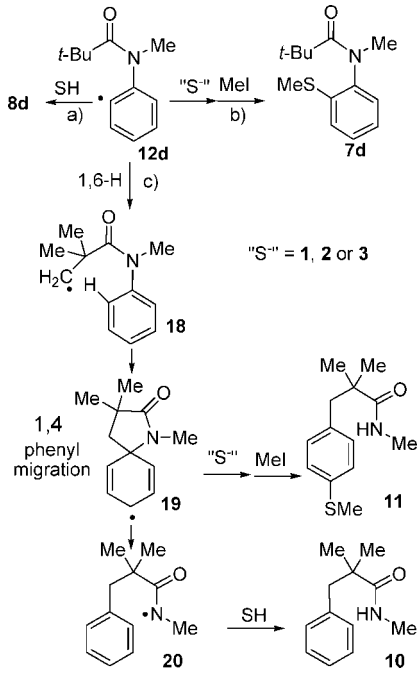
Finally, iodide **4d** reacted by photostimulation with anion **1** to yield a mixture of unrearranged (**7d** and **8d**) and rearranged (**10** and **11**) products (Table 2). The same compounds were also observed for the PET reactions with the sulfur-centered anions **2** and **3** under *entrainment* conditions. These results can be

(11) The reaction of *N*-(1-bromonaphthalen-2-yl)-*N*-methylbenzamide with thiourea anion in DMSO afforded, after 3 h of irradiation and quenching with MeI, the substituted methylthio derivative in only 11% yield with a conversion of 30% (from the recovered substrate). In this case, the unpaired spin distribution in the radical anion intermediate localizes mainly at the p PhCO system with a small but detectable density on the bromonaphthyl moiety.

(12) Baumgartner, M. T.; Jiménez, L. B.; Pierini, A. B.; Rossi, R. A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1092–1097.

(13) The lack of observation of coupling product indicates at least a ratio $[ArH]_f/[ArNu]_f = 100$ (where ArH and ArNu are the concentrations of the reduction and substitution products at time *t*). Thus, the ratio between the rate constants for the 1,5-H transfer and for the addition step shoul be $k_{1-5\text{-H}}/k_c = 100[Nu^-]_o$, where $[Nu^-]_o$ is the initial concentration of the nucleophile. Taking into consideration that the concentration of the nucleophile is 0.5 M, the rate constant for the 1,5-hydrogen migration should be at least 1 order of magnitude higher than the rate constant for the addition of thiourea anion to the aryl radical. The rate constant for coupling with thiourea anion can be estimated around $5 \times 10^7\ M^{-1}\ s^{-1}$; this considering that PhS^- is 5.1 times more reactive than thiourea anion (ref 5b) and that the rate constant determined for the coupling of *o*-(ω-alkenyl)phenyl radical with PhS^- anion is $2.6 \times 10^8\ M^{-1}\ s^{-1}$. Beckwith, A. L. J.; Palacios, S. M. *J. Phys. Org. Chem.* **1991**, *4*, 404–412. For a similar 1,5 hydrogen migration, a value higher than $10^8\ s^{-1}$ was suggested (ref 8).

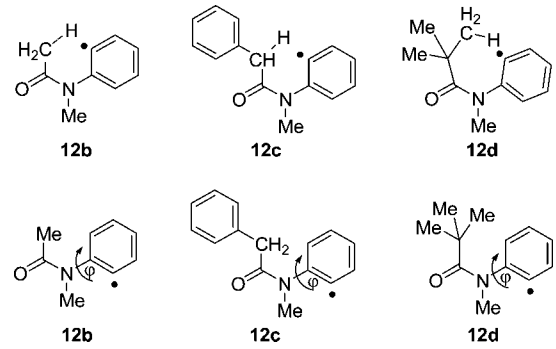
SCHEME 4



explained as follows: aryl radical **12d** (R = *t*-Bu) generated by PET (Scheme 1) has three competitive reaction pathways, as summarized in Scheme 4: (a) hydrogen atom abstraction from the solvent to yield the reduction product **8d**; (b) coupling with sulfur anions (**1**, **2**, or **3**) at the ipso position to give methylthio derivative **7d**, after quenching with MeI; and (c) 1,6-hydrogen transfer to render a primary radical (**18**), followed by a 1,4-aryl migration through the intermediacy of a spiro radical **19** to afford an amidyl radical (**20**). This nitrogen-centered radical can be reduced by hydrogen atom abstraction from the medium to give the rearranged amide **10**, the main product of this reaction.[14] In addition, further evidence of the intermediacy of the spiro radical **19** is also provided by the formation of the *para*-substituted methylthio derivative (**11**). Coupling reaction of sulfur anions **1**, **2**, or **3** at the *para* position of the spiro radical **19**, followed by fragmentation, proton transfer, and ring opening of the spiro, affords a thiolate anion. Quenching with MeI after irradiation finally yields the *p*-methylthio substituted product **11**.

Radical aryl migration reactions are well-known processes, the most extensively investigated example of 1,2-aryl migration being the neophyl-type rearrangement.[15] In the literature, there are also many examples of 1,4 and 1,5-aryl migration reactions from carbon to carbon. Nevertheless, few examples are known involving aryl migration between nitrogen and carbon atoms, for example, the 1,4-aryl migration from nitrogen to an aryl radical to yield an amidyl radical[16] and the 1,4-aryl migration from nitrogen to primary carbon radicals in the reactions of

SCHEME 5



N-arylated sulfonamides with Bu_3SnH/AIBN.[17] Recently, an unusual 1,3-aryl migration from a nitrogen to a carbon atom to afford an amidyl radical has been reported.[18] To the best of our knowledge, we here report for first time a radical 1,4-phenyl migration from a nitrogen to a primary carbon radical to afford an amidyl radical **20**. The yield of amide **10** increased to 70% when the photoinduced reaction of iodide **4d** was performed in the presence of only the enolate anion of cyclohexenone as an electron donor.

In addition, the rate constant for this novel rearrangement from **12d** to **20** (k_r, pathway c, Scheme 4) can be evaluated in DMSO using the nucleophilic addition step (pathway b, Scheme 4) as a competitive reaction. Once the yields from the substitution (ArNu = **7d**) and the rearranged reduced (Ar′H = **10**) products were determined in the photoinduced reactions of **4d** with ion **1** in excess, in order to estimate the rate constant for the rearrangement (k_r) equation 10 can be used (Table 2).[19]

$$\frac{k_r}{k_{c\text{-}\mathbf{1}}} = \frac{[Ar'H]_t[Nu^-]_o}{[ArNu]_t} \qquad (10)$$

Therefore, for the reaction with thiourea anion (**1**, 0.5 M), $k_r = 1.9\ k_{c\text{-}\mathbf{1}}$ in DMSO at 25 °C, where $k_{c\text{-}\mathbf{1}}$ is the rate constant for the coupling reaction between **1** and the *o*-substituted phenyl radical. Due to steric effects, the $k_{c\text{-}\mathbf{1}}$ for the *o*-(*N*-methylpivalamide)aryl radical (**12d**) is expected to be slower that the rate constant for the coupling of an *o*-alkenyl or the *o*-(*N*-methyl-2-phenylacetamide)aryl radical (**12c**).[13] Thus, considering that the reactivity of thiourea anion toward **12d** should be inferior to $5 \times 10^7\ M^{-1}\ s^{-1}$, a superior limit of $10^8\ s^{-1}$ (DMSO at 25 °C) can be estimated for the rate constant for rearrangement of **12d** to **20**. This rearrangement involves the individual contribution of the 1,6-H transfer, the formation of the spiro radical **19**, and finally, the ring opening to afford the amidyl radical **20**.

The experimental findings were further investigated by a theoretical gas-phase study of the energetic of the intramolecular hydrogen transfer in radicals **12b**−**d** and the barriers for rotation of the radical center around the C_{Ph}−N bond (φ dihedral, see the Supporting Information) at the B3LYP/6-31+G* level (Scheme 5).

The most stable conformations of radicals **12b** and **12d** characterize by the proximity of the radical center to the H atoms

(14) The intramolecular 1,6-hydrogen abstraction from the *ortho* aromatic carbon atom to the amidyl radical to afford an aryl radical is not a thermodynamically favorable process. The absence of labeled product **10**, when the reaction was performed in DMSO-d_6, further supports this statement.

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(19) $[Nu^-]_o$ is the initial concentration of the nucleophile; Ar′H and ArNu are the concentrations of the rearranged reduction and substitution products at time *t*. These equations are based on the assumption that the reactions of the aryl radicals with the nucleophiles and the solvent are first order in the latter species and their concentrations are constant during the experiments.

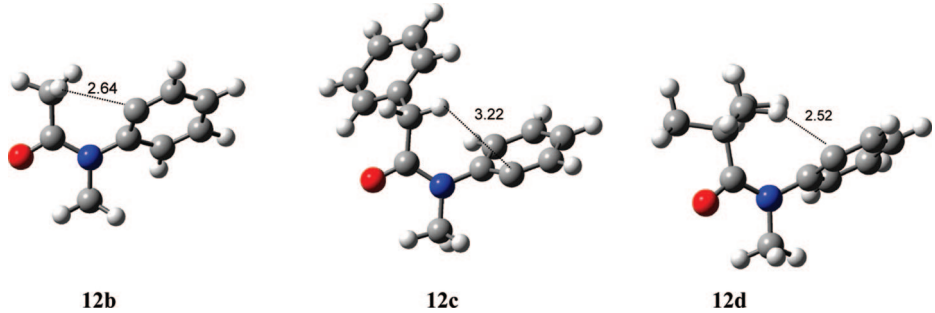

FIGURE 2. B3LYP/6-31+G* most stable conformations for radicals **12b**−**d**. Shortest radical center−hydrogen distance (Å).

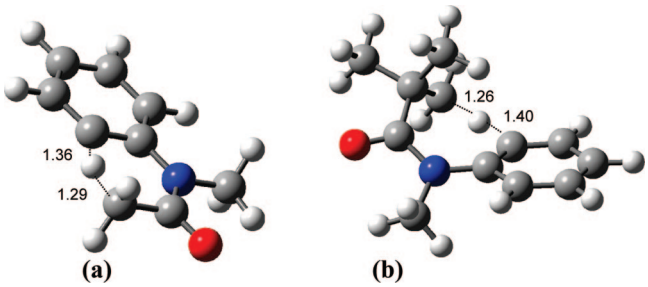

FIGURE 3. B3LYP/6-31+G* hydrogen-transfer TSs calculated for (a) **12b** and (b) **12d**. Distances of CH distinguished coordinates (Å).

of the alkyl group (Figure 2). The difference in energy between these conformations and those in which the radical is more available for coupling with a nucleophile is in the order of 0.1 and 0.9 kcal/mol for **12b** and **12d**, respectively (see the Supporting Information). On the other hand, the most stable conformation of **12c** characterizes by an appropriate disposition of the radical toward coupling (Figure 2). The stability of this conformation can be ascribed to an interaction between both phenyl rings.

The activation barriers evaluated for hydrogen transfer follow the order **12b** (5.41 kcal/mol) > **12d** (3.56 kcal/mol) > **12c** (1.46 kcal/mol), the exothermicity of the reaction being **12c** (−31.37 kcal/mol) > **12b** (−16.06 kcal/mol) > **12d** (−14.16 kcal/mol). The 1,5- and 1,6-H transfer transition states (TSs) calculated for **12b** and **12d**, respectively, are presented in Figure 3, as representative.

As seen, the 1,5-H transfer in **12c** is a highly exothermic reaction accompanied by the lowest activation energy. So, despite the most stable conformation of this radical has an appropriate geometry for coupling, the 1,5-H transfer is the favored pathway, and in agreement with the experimental findings, **12c** affords **8c** through the intermediacy of radical **17**.

The 1,6-H transfer in **12d** occurs through a cyclic 7-membered TS stabilized by a distorted boat arrangement (see Figure 3). The conformer of **12d** that prevails under equilibrium has the adequate geometric disposition for 1,6-H transfer. Moreover, the radical center is surrounded by two proximal Me groups, and thus, the reaction proceeds exothermically with low activation energy to afford radical **18**. In the latter intermediate, the radical center, at 2.79 Å from the substituted C_{Ph}, has a favorable spatial arrangement toward cyclization to render radical **19**. This addition to give the spiro-radical **19** occurs exothermically (−13.4 kcal/mol) with an activation barrier of 3.9 kcal/mol (Figure 4).

This cascade of exothermic intramolecular reactions is thus responsible of the experimental profile shown for compound **4d** which mainly affords the rearranged amide **10**.

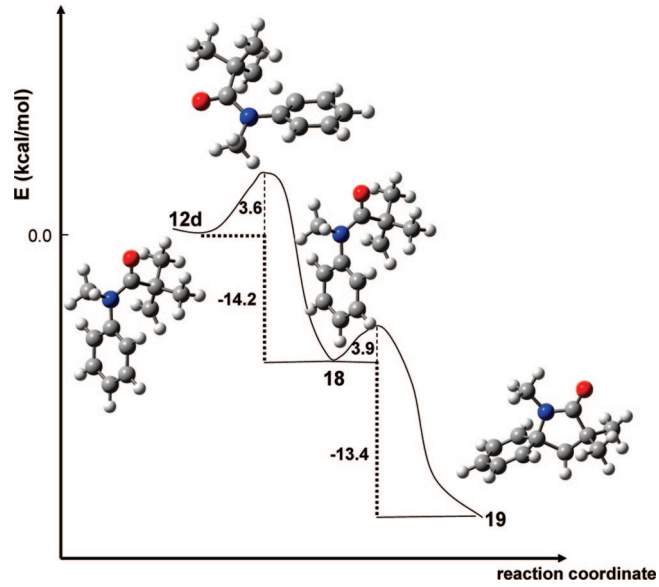

FIGURE 4. B3LYP/6-31+G* potential energy surface for the reaction **12d** → **18** → **19**.

Comparison of the activation energy for hydrogen transfer of the three radicals point the 1,5-H transfer of radical 1**2b** to require the highest activation energy. The reaction occurs through a cyclic 6 member TS in which a planar geometry is retained (see Figure 3). Despite the conformers for hydrogen transfer and nucleophile coupling have similar probability distribution at equilibrium, substitution is the main reaction followed by this radical. This result indicates that for **12b** coupling with anion **1** competes efficiently with the 1,5-H transfer.

Conclusion

o-Iodoanilides react by PET with thiourea anion (**1**), the enolate anion from cyclohexenone (**5**), or *tert*-butoxide anion (**6**) to afford *o*-amidoaryl radical (**12**) after fragmentation. The use of the enolate anion **5** under photostimulation is a good alternative to generate aryl radicals by PET under mild conditions (room temperature, irradiation with a medium-pressure Hg lamp, soft basic conditions, etc.).

For radical **12**, different reaction channels are possible depending on the structure of the alkyl substituent α to the carbonyl group: for *o*-(*N*-methylacetamide)aryl radical (**12b**), coupling with sulfur anions **1**, **2**,or **3** is the main reaction to render, after quenching with MeI, the ipso-substituted methylthio derivative in excellent yield. On the other hand, *o*-(*N*-methyl-2-phenylacetamide)aryl radical (**12c**) gives only the stabilized α-carbonyl benzyl radical by 1,5-hydrogen transfer,

which is reduced by hydrogen abstraction. Finally, *o*-(*N*-methylpivalamide)aryl radical (**12d**) affords a novel rearrangement to an amidyl radical by a 1,6-hydrogen transfer, followed by a 1,4-aryl migration through a spiro radical intermediate. Aryl radical intermediate **12d** can also give the ipso-substituted methylthio derivative and the unrearranged reduction compound as minor products. Taking into account the magnitude of the rate constant for the coupling reaction between thiourea anion and aryl radicals, a superior limit of 10^8 s^{-1} (DMSO at 25 °C) can be estimated for the rate constant for rearrangement of **12d** to **20**.

The B3LYP functional succeeds to predict the intramolecular rearrangements of the radicals proposed as intermediates. The calculations indicate that the kinetically and thermodynamically preferred reaction pathway for **12c** is 1,5-H transfer, while for radical **12d** the formation of the main experimental products, ascribed to a 1,6 H transfer followed by a 1,4 phenyl migration, is possible due to a sequence of two exothermic steps.

In view of the results herein reported, the use of *o*-iodoanilides with sulfur-centered nucleophiles is not an appropriate alternative for the synthesis of benzothiazole derivatives, due to competitive hydrogen atom transfer and radical rearrangement reactions.

Experimental Section

Chemicals. *t*-BuOK, $SC(NH_2)_2$, MeCOSK, Na_2S, 2-iodoaniline, 2-chloroaniline, cyclohexenone, *p*-dinitrobenzene, TEMPO, DTBN, *N*-methyl-*N*-phenylacetamide (**8b**), *N*-methyl-*N*,2-diphenylacetamide (**8c**), and MeI were all high purity commercial samples which were used without further purification. DMSO was distilled under vacuum and stored over molecular sieves (4 Å). Anion **1** and the cyclohexenone enolate anion were generated in situ by acid−base deprotonation using *t*-BuOK. *N*-Methylanilides **4a**−**d** and **8** were synthesized by standard procedures from the reaction between commercial 2-haloanilines and the corresponding acid chloride in CH_2Cl_2 in the presence of pyridine.[20]

All the reaction products were isolated by radial chromatography from the reaction mixture and characterized by ^1H and ^{13}C NMR and mass spectrometry. The known substrates **4a**,[21] **4b**,[22] **4c**,[23] **8d**,[24] and **9**[6b] exhibited physical properties identical to those reported in the literature.

Representative Experimental Procedure. The reactions were carried out in a 10 mL three-necked Schlenk tube, equipped with a nitrogen gas inlet and a magnetic stirrer. The tube was dried under vacuum, filled with nitrogen, and then charged with dried DMSO (10 mL). *t*-BuOK (280.5 mg, 2.5 mmol), potassium thioacetate (285.5 mg, 2.5 mmol), and aryl halide (0.5 mmol) were added to the degassed solvent under nitrogen. After 3 h of irradiation with a medium-pressure Hg lamp emitting maximally at 365 nm, the reaction was quenched by addition of MeI (342 μL, 5.5 mmol) and water (30 mL), and the mixture was extracted with methylene chloride (3 × 20 mL). The organic extract was washed twice with water and dried over anhydrous $MgSO_4$, and the products were quantified by GC by the internal standard method or isolated by radial chromatography from the crude product reaction mixture.

***N*-(2-Iodophenyl)-*N*-methylpivalamide (4d)[25]:** white solid; mp 132.4−133.4 °C; ^1H NMR (400.16 MHz, $CDCl_3$, 30 °C) δ = 1.06 (s, 9H, $C(Me)_3$), 3.16 (s, 3H, NMe), 7,04 (ddd, 1H, Ar-H, J_o = 7.56, J_o = 7.64, J_m = 1.60), 7.28 (dd, 1H, Ar-H J_o = 7.64, J_m = 1.60), 7.38 (ddd, 1H, Ar-H, J_o = 8.04, J_o = 7.56, J_m = 1.40), 7.90 (dd, 1H, Ar-H, J_o = 8.04, J_m = 1.40); ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C) δ 29.2, 39.8, 40.9, 129.2, 129.4, 140.1, 140.1, 147.5, 177.8; the assignments are supported by COSY 45 and HSQC spectra; GC/MS (EI) (*m*/*z*) 57 (100), 77 (14), 104 (13), 139 (9), 166 (5), 190 (73), 233 (14), 260 (2); HRMS (electrospray) calcd for $C_{12}H_{17}INO$ 318.0349 $(M + H)^+$, found. 318.0356.

***N*-Methyl-*N*-(2-(methylthio)phenyl)acetamide (7b).** white solid; ^1H NMR (200 MHz, $CDCl_3$, 30 °C) δ 1.80 (s, 3H, COMe), 2.45 (s, 3H, SMe), 3.18 (s, 3H, NMe), 7.11−7.43 (m, 4H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$, 30 °C) δ 14.0, 21.7, 35.0, 124.9, 125.4, 128.1, 128.8, 138.4, 141.2, 170.8; the assignments are supported by COSY 45 and HSQC spectra; GC/MS (EI) (*m*/*z*) 195 (5, M^+), 148 (100), 138 (29), 122 (10), 109 (9), 94 (22), 77 (13), 51 (6); HRMS (EI) calcd for $C_{10}H_{13}NOS$ 195.07179 M^+, found 195.07217.

***N*-Methyl-*N*-(2-(methylthio)phenyl)pivalamide (7d):** white solid; mp 80.5−81.3 °C; ^1H NMR (200 MHz, $CDCl_3$, 30 °C) δ 1.06 (s, 9H, *t*-Bu), 2.45 (s, 3H, SMe), 3.14 (s, 3H, NMe), 7.11−7.37 (m, 4H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$, 30 °C) δ 14.1, 28.9, 38.9, 40.9, 124.7, 128.9, 129.1, 139.0, 141.9, 178.6; the assignments are supported by COSY 45, HSQC and HMBC spectra; GC/MS (EI) (*m*/*z*) 190 (100), 180 (9), 153 (9), 134 (18), 133 (14), 120 (3), 94 (4), 77 (4), 57 (60); HRMS (electrospray) calcd for $C_{13}H_{20}NOS$ 238.1260 $(M + H)^+$, found 238.1265; IR (KBr) ν (cm^{-1}) 1633, 1354.

2-Benzyl-*N*,2-dimethylpropanamide (10): white solid; mp 79−80 °C; ^1H NMR (400.16 MHz, $CDCl_3$, 30 °C) δ 1.18 (s, 6H, $C(Me)_2$) 2.73 (d, 3H, NMe) 2.84 (s, 2H, CH_2), 5.46 (s, 1H, NH), 7.11−7.28 (m, 5H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$, 30 °C) δ 24.8, 26.1, 43.1, 46.6, 126.0, 127.6, 129.8, 137.9, 177.3; the assignments are supported by COSY 45 and HSQC spectra; GC/MS (EI) *m*/*z* 191 (M^+, 11), 176 (20), 149 (30), 132 (5), 133 (8), 117 (14), 100 (8), 92 (19), 91 (100), 58 (16); HRMS (EI) calcd for $C_{12}H_{17}NO$ 191.13101 (M^+), found 191.13077; IR (KBr) ν (cm^{-1}) 3293, 1633, 1555.

2-(4-(Methylthio)benzyl)-*N*,2-dimethylpropanamide (11): white solid; mp 95.0−95.3 °C; ^1H NMR (400.16 MHz, $CDCl_3$, 30 °C) δ 1.16 (s, 6H, $C(Me)_2$), 2.46 (s, 3H, SMe), 2.72 (d, 3H, NMe), 2.77 (s, 2H, CH_2), 5.44 (s, 1H, NH), 7.03 (d, 2H, J = 8,42), 7.13 (d, 2H, J = 8.42); ^{13}C NMR (100,62 MHz, $CDCl_3$, 30 °C) δ 15.9, 25.1, 26.4, 43.5, 46.4, 126.3, 130.6, 135.2, 136.1, 177.5; the assignments are supported by COSY 45, HSQC and DEPT 135 spectra; CG/MS (EI) *m*/*z* 237 (M^+, 29), 179 (5), 137 (100), 122 (7), 91 (5), 58 (7); HRMS (EI) calcd for $C_{13}H_{19}NOS$ 237.11873 (M^+), found 237.11820; IR (KBr) ν (cm^{-1}) 3337, 1633, 1540.

Computational Procedure. All calculations were performed with the Gaussian03 program, the B3LYP[26] DFT functional, and the LANL2DZ basis set for iodine-containing compounds. This effective core potential (ECP) basis set[27] was previously used in the evaluation of the anionic surfaces of halobenzenes and afforded results of acceptable quality to compare the electronic properties of PhI with respect to PhX (X = F, Cl, Br).[28] The 6-31+G* basis set was used to study all of the remaining systems.

The characterization of stationary points was done by Hessian matrix calculations. The effect of DMSO as polar aprotic solvent was evaluated through Tomasi's Polarized Continuum Model (PCM)[29] as implemented in Gaussian03. The energy informed

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for TSs and radicals includes zero-point corrections. The calculations related to the radicals were performed in the gas phase.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR of compounds **4d**, **7b**,**d**, **10**, and **11**. COSY 45 and HSQC or HMBC spectra to support the assignments. *xyz* coordinates and total energies in atomic units of the species calculated. This material is available free of charge via the Internet at http://pubs.acs.org.

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