Perfluorobutylation of benzo(hetero)arenes in aqueous media

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ABSTRACT

Perfluorobutylation of a series of benzo(hetero)aromatic compounds without formal leaving groups is achieved efficaciously in organic solvent-water mixtures under photostimulation. The methodology is compared with previously reported trifluoromethylation strategies of these nuclei in terms of product yields and regioselectivity. The reaction is a radical homolytic aromatic substitution process, where the perfluoroalkyl-substituted cyclohexadienyl radical intermediate is first oxidized and then a proton transfer sequence leads to the products.

Keywords: radical reactions in aqueous media, C-H perfluoroalkylation, homolytic aromatic substitution, perfluoroalkylation, dibenzoheteroarenes.

1. INTRODUCTION

A distinct division between innate perfluoroalkylation reagents, which accomplish substitution of aromatic nuclei without formal leaving groups, and those which substitute functionalized aromatic substrates can be established [1]. Among the former, the Langlois reagent [2], NaSO2Rf, has intensively been used under mild radical initiation conditions with tBuOOH affording perfluoroalkyl-substituted aromatic compounds in good yields in aqueous media.

Togni and collaborators have achieved the trifluoromethylation of a series of heteroaromatic compounds employing the hypervalent iodine reagent 1-(trifluoromethyl)-1,2-benziodoxol-3-(1H)-one (I) (Scheme 1) and methyl trioxorhenium as catalyst [3]. Very recently, this reagent (I) has been employed in the perfluoroalkylation of phenanthridines through a radical mechanism using dioxane as solvent, in the absence of methyltrioxorhenium catalyst [3]. A review article highlighting important examples of radical trifluoromethylation and perfluoroalkylation reactions making use of these new reagents has recently been published [4]. Photocatalysts have also been employed to accomplish homolytic perfluoroalkylation reactions of aromatic and heteroaromatic compounds in organic solvents [5].

A photochemical method for achieving radical perfluoroalkylation reactions of aromatic nuclei in water and aqueous media through an ion-radical chain sequence, with aromatic compounds without formal leaving groups has recently been discussed [6]. This methodology turned out to be very suitable for electron-rich aromatic substrates, where an electron transfer (ET), and then proton transfer (PT) steps afford the substitution products.

We herein present a photoinduced method to obtain a direct C-H perfluorobutylation reaction of benzo(hetero)arenes in aqueous media, as a novel addition to the synthesis methods of perfluoroalkyl-substituted fused aromatics and heteroaromatic nuclei of biological and technological relevance. This methodology circumvents the use of transition metal reagents or catalysts and uses mild initiating techniques.

2. EXPERIMENTAL SECTION

Most of theseparation, irradiation, and purification procedures used in this study have been reported earlier [6].Some of the preparative TLC techniques employed a fluorous phase system, consisting of a mixture of 1-methyl-perfluorodecaline:iso-octane (1:1). NMR analyses were performed using CDCl3 as solvent or as noted otherwise. 2D-NMR experiments performed to assign 1H-1H, and 1H-13C connectivities include COSY-45, HSQC, HMBC, and HOESY and NOESY techniques. Irradiation of mixtures was carried out under conditions where only primary photoproducts were obtained, and in most cases the total substrate conversion was kept lower than 45%.

3-perfluorobutyl-1H-indole (6): Yellow oil, 17%, 6.1 mg. 1H-NMR (500 MHz, CDCl3) δH ppm: 8.69 (s, 1H), 7.68 (d, J= 7.6 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.44-7.50 (m, 2H) and 7.11 (s, 1H). 13C-NMR (125 MHz, CDCl3) δC ppm: 137.5, 132.1, 126.1, 125.7, 124.7, 121.8, 116.2 and 106.2. MS EI (70 eV) m/z (%): 335 (24), 167 (17), 166 (100), 83 (12) and 69 (11). 19F-NMR (470.4MHZ, CDCl3) δF (ppm): - 80.06, - 108.70, - 123.13 and

Scheme 1. Usage of Togni´s reagent and methyl trioxorhenium as catalyst for the trifluoromethylation of heteroaromatic compounds.

2-perfluorobutyl-1H-indole (7): Yellow oil, 8%, 3.1 mg. 1H-NMR (500 MHz, CDCl3) δ ppm: 8.43 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.44-7.50 (m, 1H), 3.75 (t, J = 7.9 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H) and 3.68 (s, 2H). 13C-NMR (125 MHz, CDCl3) δ ppm: 137.4, 131.1, 129.2, 125.5, 122.5, 121.6, 120.4 and 106.9. 19F-NMR (470.4 MHz, CDCl3) δ ppm: -80.98, -109.21, -122.46, -126.11. Did not ionize in HRMS (ESI-TOF).

2-(perfluorobutyl)-1H-indene (10). Yellow Oil 66% yield, 44.2 mg. 1H-NMR (500 MHz) δ ppm: 8.09 (d, 1H), 7.90 (d, 1H), 7.63 (d, 1H) and 7.48 (dt, 1H). 13C-NMR (125 MHz) δ ppm: 141.7, 136.6, 131.9, 129.6, 126.6, 126.3 and 125.7. 19F-NMR (470.55 MHz, CDCl3) δ ppm: -80.79, -102.33, -122.12 and -125.69. Did not ionize in HRMS (ESI-TOF).

3-(perfluorobutyl)-1H-indole and 3-(perfluorobutyl)-benzo[b]thiophene. Trifluoromethylation of 1H-NMR (500 MHz) δ ppm: 8.10 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.25 Hz, 1H), 7.63 (d, 1H), 7.50 (d, 1H) and 7.47 (dt, 1H). 13C-NMR (125 MHz) δ ppm: 141.3, 138.1, 138.0, 134.4, 127.9, 127.9, 124.2 and 124.0. 19F-NMR (470.55 MHz, CDCl3) δ ppm: -80.79, -102.11, -122.12 and -125.69. Did not ionize in HRMS (ESI-TOF).

3. RESULTS SECTION

When 1H-indole 1 is made to react (254-nm irradiation, 1 h) with n-C4F9I in a mixture of MeCN:H2O, we obtained the expected 3-perfluorobutyl-1H-indole (product 6, Scheme 1). Along with this product, the 2-substituted perfluorobutyl-indole was also observed (product 7, Scheme 1, Table 1, entry 1). However, the overall isolated substitution yield was rather low, that is 25%. Both products, 6 and 7, were obtained in a relative ratio of 66:33, respectively. Indole 1 was recovered in 72% isolated yield.

Further conversion of the starting material led to secondary photoproducts. In order to optimize reaction conditions, we varied the substrate and n-C4F9I concentrations with the purpose of maximizing product yields. This was achieved through plotting percent substitution product versus n-C4F9I or substrate concentration at 254-nm irradiation (not shown) and obtained the best results as shown in column 3, Table 1. When reaction conditions are such that the absorption of substrates prevails at 254-nm wavelength, very low yields of substitution products were obtained. The highest substitution product yields were obtained when n-C4F9I was in excess with respect to substrate. When we subjected N-methyl indole 2 instead of 1H-indole 1 to the photoreaction in aqueous media with n-C4F9I, we obtained the perfluorobutyl-substituted product at the 2- (product 8) position of the ring in 35% yield. Product 8 was characterized by standard spectroscopic techniques. Indole 2 was recovered in 61% isolated yield. Further conversion of the starting material led to secondary photoproducts. Trifluoromethylation of 1H-indole and N-methyl indole at the 2-,3-, and 7- positions has recently been achieved by Togni and collaborators [7, 8] using CHCl3 as solvent (Scheme 1). Their protocol renders a mixture of the 2-,3-, and 7-CF3-substituted regioisomers that could not be separated, but identified by 19F NMR spectroscopy as the isomeric mixture. (Do you mean another methodology has recently been reported by Xiao et al. for the trifluoromethyl ipso-substitution of indole employing DMF as solvent [9].)
When we subjected benzofuran 3 to react under photostimulation (254 nm) with n-C₄F₉I in MeCN:H₂O mixture, we exclusively obtained 2-(perfluorobutyl)-benzofuran 9 in 90% yield, as shown in Table 1, entry 3 (Scheme 2). Recently, Togni and collaborators have accomplished the trifluoromethylation of benzofuran and their heteroanalogues at the 3- and 2- positions with the Togni’s reagent, and methyltrioxorhenium as catalyst (Scheme 1)[7]. Their methodology, however, is not regioselective and renders the mixture of regioisomers that could not be separated but characterized by spectroscopic methods. 3-Trifluoromethyl-benzofuran has recently been synthesized by Sanford and collaborators using benzofuran-2-ylboronic acid (a functionalized benzofuran ring) in the presence of NaSO₂CF₃, tert-butylhydroperoxide (TBHP) and a copper salt in 89% yield [10]. The photoinduced methodology, under our reaction conditions, seems to provide selectively the 2-substituted perfluorobutyl benzofuran isomer in excellent yield (innate perfluoroalkylation). When 1-H-indene 4 is made to react (254 nm) under similar reaction conditions, product 10 (Scheme 2, Table 1, entry 4) was obtained in 66% yield. Gassman and colleagues [11] have reported that the 2-perfluoroalkyl-substituted indene product could be obtained through a photoinduced perfluoroalkyl iodide addition that could not be isolated, but decomposed in-situ to the 2-perfluoroalkyl-substituted indene product through base-promoted dehydroiodination. Under our reaction conditions, however, no base was utilized to obtain product 10, and the pH decreased gradually throughout the course of the reaction (Table 1, column 6). Benzothiophene 5 was also substituted to the photoinduced (254-nm) perfluorobutylation reaction in MeCN:H₂O to yield a mixture of regioisomers substituted at the 2-, (product 11), 3-, (product 12), and 7-, (product 13) positions of the benzothiophene ring with the C₄F₉ moiety in 49% overall yield that could not be isolated as single regioisomers but characterized in the reaction mixture (Table 1, entry 5) by multidimensional NMR techniques. These isomers (2-, 3-, and 7- C₄F₉ substituted benzothiophenes) were obtained in a relative ratio of 43:30:27, respectively. Togni and collaborators [7] attained the trifluoromethylation of benzothiophene with the Togni’s reagent, affording a mixture of the 2-, 3-, and 7-C₄F₉ substituted regioisomers (innate trifluoromethylation, Scheme 1). However, this mixture of isomers could not be separated. Sanford and collaborators selectively synthesized the 2-trifluoromethylbenzothiophene from benzothiophene-2-ylboronic acid (a functionalized benzothiophene ring) in the presence of NaSO₂CF₃, tert-butylhydroperoxide (TBHP) and a copper salt in 77% yield [10]. A minor isomer, accounting for less than 1% of the total yield of the mixture could be distinguished by the ¹H NMR spectrum of the chromatographed reaction mixture, which seems to correspond to another C₄F₉-regioisomer. Through a combination of 2D-NMR techniques, full spectral characterization of this isomer was possible in the mixture, and the identity of the compound was assigned as 6-(perfluorobutyl)-benzothiophene 14. No ring-opening product was observed from the photoreactions of 1-5 with n-C₄F₉I under our reaction conditions. Addition of n-C₄F₉I provokes a decrease in fluorescence intensity, as observed in the Stern-Volmer plots (not shown). This quenching of fluorescence is in agreement with an electron-transfer process within the solvent cage, as has been proposed before [6]. The pH was monitored throughout the reaction for compounds 1-5, (column 6, Table 1) with n-C₄F₉I either at 350-nm or at 254-nm irradiation. A significant decrease in pH was observed in all cases, as reaction progresses. Table 1, column 6 depicts the pH at the beginning and end of the reaction. This evidence is in accordance with a proton release in the course of the reaction, such as that observed in classical aromatic electrophilic substitution reactions, S₈Ar.

Addition of di-tertbutyl nitroxide (DTBN, 2% equiv), a well-known radical scavenger, at 254-nm irradiation in MeCN:H₂O mixtures, provoked a retardation of the reactions, purporting the presence of radicals as intermediates. Addition of p-dinitrobenzene(β-DNB), a known radical anion scavenger, did not affect the yields of the perfluoroalkyl group substitutions of the dibenzoarenes. The photoreactions carried out under basic conditions (pH ~ 10) did not show an enhancement in product yields. This would seem to imply that radical anions are not intermediates in these reactions. When 4-nitrodibenzofuran 15 was allowed to react with n-C₄F₉I in MeCN:H₂O mixtures either under 254-nm or 350-nm irradiation conditions, no substitution products were observed (Table 1, entry 6). In previous photoinduced substitutions studies with RfI [6] employing N,N-dimethyl-1-naphthylamine (DMNA) in water, we were able to detect the radical cation of DMNA in the presence of n-C₄F₉I from the UV-vis transient spectra obtained by Nanosecond Laser Flash Photolysis techniques at 355 nm excitation. This indicated an ET process to yield the radical cation of the substrate, and hence the dissociative radical anion of RfI, under reaction conditions where absorption of aromatic substrates prevail.

![Scheme 3. Proposed mechanism for the perfluorobutylation of benzo(hetero)arenes in aqueous mixtures.](image)

Given the acceptor properties of RfI, and the donor abilities of substrates 1-5, a photoinduced ET sequence could be in operation, such as that postulated for aromatic amines [6]. The fact that 4-nitrodibenzofuran 15 does not react under our reaction conditions, might be indicative of the scarce electron donor ability of nitroarenes, or the poorly-stabilized Wheland intermediate. Notwithstanding, in the present study, when reaction conditions were changed to those where absorption of substrates ((hetero)arenes) prevail at 254-nm irradiation wavelength as
opposed to absorption of n-C4F9I (conditions where PET could take place), very low yields of substitution products were obtained. By increasing the amounts of n-C4F9I in the reaction mixtures, a steady increase in substitution product yield was suggested, indicating that the reaction is initiated through homolysis of F3C-C¼I bond leading to C4F9 free radicals, and further homolytic radical substitution of the benzo(hetero)arene. Indication of the proton release, is consistent with a (hetero)cyclohexadienyl-type radical intermediate that undergoes oxidation to a Wheland intermediate (σ-adduct).

At 254-nm irradiation, where most of the light is absorbed by n-C4F9I (see Table 1, column 6, footnote b), homolysis of F3C-C¼I bond produces perfluorobutyl radicals that add to the benzo(hetero)arene as in Scheme 3 below, to yield the radical adduct intermediate A. The radical adduct A undergoes a sequence of ET to n-C4F9I (to afford cation intermediate B, Wheland intermediate, oxidation triggered through the favorableGibbs energy) and then the proton transfer (PT) steps to yield the substitution products in averaged good yields. We postulate that this mechanism is likely operative for substrates 1-5.

**Table 1.** Optimized reaction conditions tested in the Hydrogen atom substitution (HAS) reaction of arenes with perfluoroalkyl halides in heterogeneous media under vigorous stirring

<table>
<thead>
<tr>
<th>Entry</th>
<th>Synthetic method</th>
<th>Substrates (mmol)</th>
<th>Solvent system, (mL)*</th>
<th>Product (%) yield</th>
<th>A_{substrate} - A_{RT} *</th>
<th>pH_{initial}/pH_{final}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>λ 254 nm</td>
<td>1 (0.2), n-</td>
<td>MeCN:H2O 1:1, (4)</td>
<td>(25) b</td>
<td>1:1</td>
<td>5.5/3</td>
</tr>
<tr>
<td>2</td>
<td>λ 254 nm</td>
<td>2 (0.2), n-</td>
<td>MeCN:H2O 1:1, (4)</td>
<td>8 (35) d</td>
<td>1:1</td>
<td>5.5/3</td>
</tr>
<tr>
<td>3</td>
<td>λ 254 nm</td>
<td>3 (0.2), n-</td>
<td>MeCN:H2O 3:1, (4)</td>
<td>9 (90) d</td>
<td>1:3:1</td>
<td>5.5/3</td>
</tr>
<tr>
<td>4</td>
<td>λ 254 nm</td>
<td>4 (0.2), n-</td>
<td>MeCN:H2O 3:1, (4)</td>
<td>10 (66) d</td>
<td>1:1</td>
<td>5.5/3</td>
</tr>
<tr>
<td>5</td>
<td>λ 254 nm</td>
<td>5 (0.2), n-</td>
<td>MeCN:H2O 3:1, (4)</td>
<td>49 (4) e</td>
<td>1:1</td>
<td>5.5/5/5.5*</td>
</tr>
<tr>
<td>6</td>
<td>MPL or λ 254 nm</td>
<td>15 (0.2), n-</td>
<td>MeCN:H2O 3:1, (4)</td>
<td></td>
<td>11 (43) e</td>
<td>5.5/2</td>
</tr>
</tbody>
</table>

*Ar-deoxygenated solutions; †Absorbance ratio at the irradiation wavelength (254 nm or 365 nm) in pure organic solvent; ‡ pH registered at the beginning of the reaction/pH registered at the end of the reaction; § isolated product yield; ¶ relative regioisomer yield; ‖ Medium pressure Hg lamp, unfiltered.

4. CONCLUSIONS

We herein present a substitution reaction on benzo(hetero)arenes in aqueous media with C4F9 moieties yielding perfluoroalkyl group-substituted compounds in moderate to good yields. It is to be noted that these aromatic compounds have never been substituted before with perfluoroalkyl moieties by a direct methodology.

5. REFERENCES


6. ACKNOWLEDGEMENTS

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