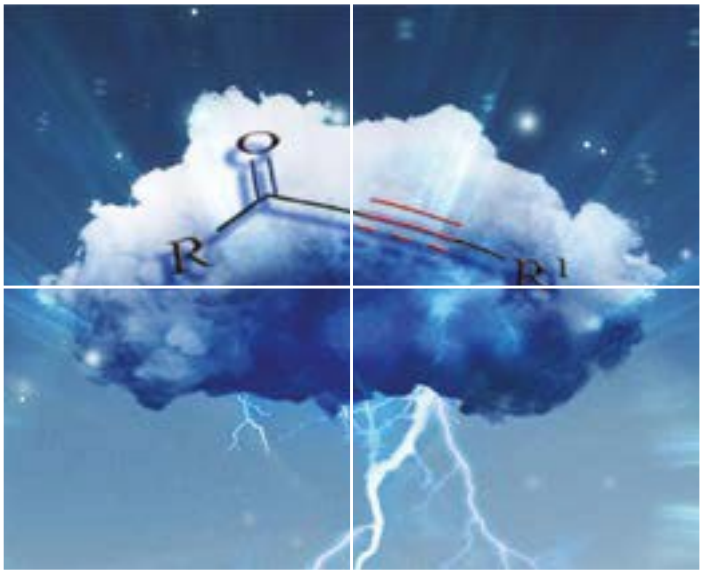
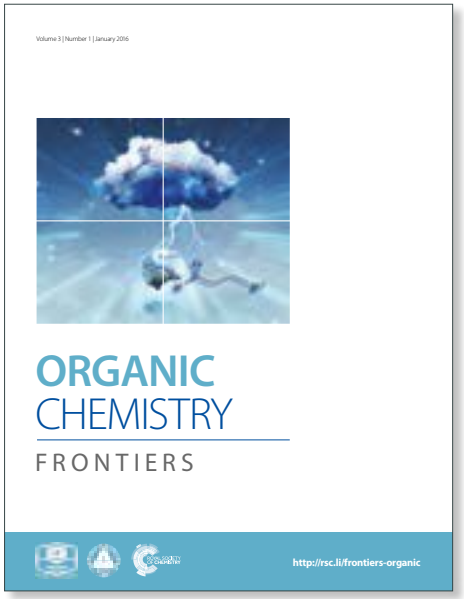
ORGANIC CHEMISTRY
FRONTIERS



Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. Soria-Castro, F. Bisogno and A. B. Peñéñory, *Org. Chem. Front.*, 2017, DOI: 10.1039/C6QO00776G.



View Article Online
DOI: 10.1039/C6QO00776G

Journal Name

ARTICLE

Versatile One-Pot Synthesis of Benzo-fused Thiacycles by Copper Catalysis

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Silvia M. Soria-Castro,[a] Fabricio R. Bisogno[a]* and Alicia B. Peñéñory[a]*

A novel one-pot synthesis of structurally diverse benzo-fused thiacycles via a Cu-catalysed intermolecular C–S coupling/cyclisation tandem process, employing the same catalytic system, has been developed. Thus, 3,4-dihydro-2*H*-benzo[*e*][1,3]thiazines and 4*H*-benzo[*e*][1,3]thiazines were selectively obtained by this one-pot tandem process from (2-iodophenyl)methanamine and aldehydes or 1-(azidomethyl)-2-iodobenzene, respectively. These reactions proceeded in toluene at 100ºC with either potassium thioacetate, thiobenzoate or ethyl xanthogenate in moderate to good isolated yields. The first one avoids the imine isolation step. A similar approach to benzo[*b*]thiophene derivatives from 2-(2-iodophenyl)acetonitrile was also developed.

Introduction

Benzo-fused thiacycles have lately attracted great attention given its paramount importance in several fields such as state-of-the-art molecular electronics,[1] tunable materials[2] and medicinal chemistry[3-6] along with other. Therefore, methods to build-up diverse benzothiacycles are rather useful and mostly rely on metal-catalysed C-S coupling of properly substituted haloarenes.[7] Among them, Cu-based protocols generally furnish the desired products with high isolated yields and readily tolerate a wide array of functional groups.[7-9] As for Pd-based methods, it is worth mentioning that for any desired scaffold to be constructed, reaction parameters must be optimised since advantageous conditions for a given thiacycle might be deleterious for another.[10] Thus, from a practical point of view a general catalytic system is highly desirable.

Besides, benzothiazines are important heterocycles present in natural products and synthetic molecules. Particularly, benzo[*e*][1,3]thiazines have shown activity as fungicidal,[3] antibiotic,[4] anti-ischemic,[5] antidepressant and psychotropic[6], making them attractive synthetic targets. 4*H*-Benzo[1,3]thiazine derivatives have been synthesised through different approaches including cyclisation of *N*-(arylthiomethyl)benzamides with $POCl_3$,[3] photocyclisation of 1,2,4-triazole-3-thiones,[11] hetero-Diels-Alder cycloaddition,[12] or reaction of aryl thioesters with substituted benzyl cyanides.[13] Regarding transition metal-based protocols, there are a few examples where Pd and Cu are used as catalysts. Recently, the one-pot synthesis of 3,4-dihydro-2*H*-benzo[1,3]thiazine-2-imines via intramolecular Pd-catalysed C–S bond formation has been developed.[14] The synthesis of aza[2,1-*b*][1,3]-benzothiazinones from cyclic thiourea and methyl 2-iodobenzoate was possible via tandem[15] Cu-catalysed intermolecular C-S coupling/amidation process.[16]

Likewise, benzothienyl motifs are found within the structural core of several pharmaceutical drugs such as raloxifene,[17] for the treatment of breast cancer and osteoporosis; zileuton used to prevent asthma attacks; and sertaconazole an antifungal drug. Several methodologies for the synthesis of benzothiophenes are known including nucleophilic substitutions followed by electrophilic cyclisation[18] or condensations,[19] Friedel Crafts acylations,[20] Grignard addition followed by heterocyclisation,[21] and transition metal catalysed heterocyclisations.[22] In particular, and although 2-amino-benzothiophene is an intermediate in the synthesis of raloxifene, its preparation continue being a challenge. In this context, we have previously described a simple procedure for the synthesis of five-membered sulfur heterocycles by reaction of inexpensive potassium thioacetate (KSCOMe) with aryl iodides under a base-free Cu/ligand catalytic system.[8a] This one-pot methodology involves a cascade of reactions with Cu-catalysed C–S bond formation as a key step for the sulfur atom installation.

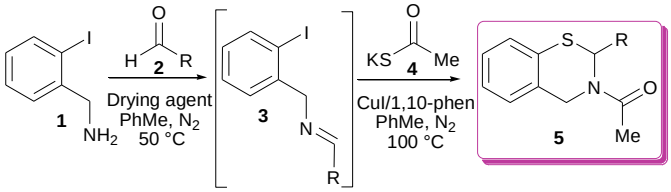
Herein we report a novel one-pot synthesis of diverse benzo-fused thiacycles via a Cu-catalysed intermolecular C–S coupling/cyclisation tandem process, employing the same catalytic system, demonstrating the robustness and versatility of this methodology. We make use of commercially available and easy-to-handle thiocarboxylic reagents, so, unstable and bad smelling thiols are avoided.[23]

[a] INFIQC, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, X5000HUA Córdoba, Argentina. E-mail: penenory@fcq.unc.edu.ar
Electronic Supplementary Information (ESI) available: Spectra (^{1}H and ^{13}C NMR) for all the new products, experimental procedures and supplementary schemes and table). See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C6QO00776G

Results and discussion

With the aim of developing a one-pot methodology to obtain benzo[*e*][1,3]thiazine derivatives **5** from (2-iodophenyl) methanamine (**1**), a procedure involving *in situ* formation of imines was set up, (Scheme 1). Therefore, as a first step, **1** and the corresponding aldehyde **2** were combined for imine **3** formations in toluene in the presence of a drying agent such as anhydrous Na_2SO_4 or 4Å molecular sieves. In a second step, KSCOMe (**4**) and the reagents for the Cu-catalysed coupling/cyclisation tandem reaction were added, according to previous optimised catalytic conditions.[8a]



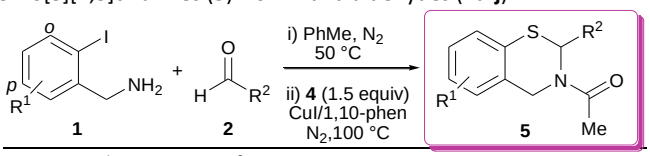
Scheme 1. One-pot two-steps synthesis of 3,4-dihydro-2*H*-benzo[*e*][1,3]thiazine (**5**) from amine **1**.

The best results were obtained without any drying agent, likely due to interference in the Cu-catalysed C-S coupling (optimised conditions not shown). To evaluate the efficiency and scope of this one-pot reaction, different aldehydes were used, as summarised in Table 1. When 4-pyridinecarboxaldehyde (**2a**) was tested, heterocycle **5a** was obtained with 48% of isolated yield after 48 h (entry 1). Similar results were observed with other aldehydes bearing electron-withdrawing groups (EWGs) in *para*-position (entries 4 and 5). Noteworthy, aldehydes bearing chloro and bromo substituents, which can be useful in further derivatisation, were also suitable in this reaction (entries 2, 3 and 8).

As noticed, when an aldehyde possessing electron-donating groups (EDGs) such as **2f** was used, **5f** was isolated (46% yield). This result is relevant for aldehydes bearing EDGs, since their low reactivity towards amine condensation reaction hindered imine product isolation. In addition, steric hindrance due to *ortho*-substitution is an important issue when the substituent poorly (if any) coordinates Cu, such as CF_3[24] or Cl. Thus, after 24h, *p*-Cl-substituted aldehyde **2c** afforded 70% yield of **5c**, while *o*-Cl-substituted aldehyde **2h** rendered heterocycle **5h** with lower yield (52%), (entries 3 and 8). Particularly remarkable is the steric effect exerted by CF_3 group.[25] In this sense, aldehyde **2j** gives only 15% isolated yield of **5j** in comparison with the *para*-analog **2g** affording 76% yield of **5g** (entries 7 and 11). Conversely, *ortho*-substitution by a MeO group in aldehyde **2i** in comparison with *para*-substituted **2f** substantially affected reaction rate, affording 64% yield of **5i** in only 24 h and 31% yield of **5f** after 24 h, respectively (entries 9 and 6). The coordinating effect of MeO group was confirmed conducting the reaction in the absence of the ancillary ligand, and 28% yield of **5i** was isolated (entry 10). This *ortho* effect accelerating the reaction by coordination has also been reported for other Cu-catalysed reactions, with *ortho*-substituted aryl halides.[26]

The *p*-F and *p*-Br substituted substrates **1b-c** afforded good yields of the dihydrobenzothiazines **5k-l**, while an important steric effect by *ortho*-methyl substitution was observed when using **1d** (entries 12 -14).

TABLE 1. One-pot synthesis of 3,4-dihydro-2*H*-benzo[*e*][1,3]thiazines (**5**) from **1** and aldehydes (**2a-j**).[a]



Entry	R^1	R^2	**5**, isolated yield (%)
1	**1a**, H	4-pyridyl (**2a**)	**5a**, 48
2		*p*-BrC_6H_4 (**2b**)	**5b**, 61[b]
3		*p*-ClC_6H_4 (**2c**)	**5c**, 70[b]
4		*p*-CNC_6H_4 (**2d**)	**5d**, 60
5		*p*-$NO_2C_6H_4$ (**2e**)	**5e**, 40[b]
6		*p*-$MeOC_6H_4$(**2f**)	**5f**, 46, 31[b]
7		*p*-$CF_3C_6H_4$ (**2g**)	**5g**, 76
8		*o*-ClC_6H_4 (**2h**)	**5h**, 52[b]
9		*o*-$MeOC_6H_4$ (**2i**)	**5i**, 64[b]
10[c]		*o*-$MeOC_6H_4$ (**2i**)	**5i**, 28[b]
11		*o*-$CF_3C_6H_4$ (**2j**)	**5j**, 15
12	**1b** *p*-F	*p*-ClC_6H_4 (**2c**)	**5k**, 78[b]
13	**1c**, *p*-Br	*p*-ClC_6H_4 (**2c**)	**5l**, 68[b]
14	**1d**, *o*-Me	*p*-ClC_6H_4 (**2c**)	**5m**, 23[b]

[a]Reaction Conditions: **1** (0.5 mmol) and **2** (0.5 mmol) in toluene (4 mL) at 50 °C for 1 h. Then, **4** (1.5 equiv., 0.75 mmol), CuI (10 mol%, 0.05 mmol) and 1,10-phenanthroline (20 mol%, 0.1 mmol) at 100 °C for 48 h. [b]24 h of reaction time. [c]In the absence of 1,10-phenanthroline.

In order to demonstrate that imino species are the actual coupling partners of KSCOMe (**4**), we synthesised and isolated the corresponding imine **3n** that was subjected to the same reaction conditions. Table 2 summarises the results. For the synthesis of imines see Supporting Information (S.I.), Scheme S1.

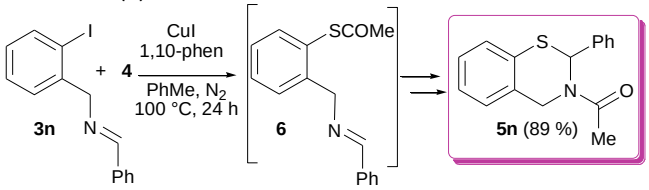
Thus, the Cu-catalysed reaction of **4** with imine **3n** afforded heterocycle 3,4-dihydro-2-phenyl-2*H*-benzo[*e*][1,3]thiazine (**5n**) in 72 % isolated yield, (Table 2, entry 1). After the initial Cu-catalysed intermolecular arylation reaction to afford aryl thioester intermediate (**6**), the latter could undergo a cyclisation reaction. Once again, *N*-acylation of the heterocycle occurred, preventing further oxidation into 2-phenyl-4*H*-benzo[*e*][1,3]thiazine derivative.

Next, some control reactions were performed for mechanistic elucidation. The coupling reaction between **4** and **3n** afforded 49 % isolated yield of **5n** at 24 h (entry 2) and did not occur under air or in the absence of the Cu source (entries 3 and 4). The reaction also proceeded, although slowly, in the absence of ligand (entry 5). This last observation indicates that the imine can coordinate Cu and assist it in the reaction. Finally, a benzyl imine analogous to **3n** lacking the halogen substituent was prepared and tested (entry 6). After 48 h a solution of *N*-benzyl-1-phenylmethanimine and **4** did not react and the imine was recovered untouched. Thus, a direct reaction of thioacetate with the imine functionality can be ruled out.

All the results shown in Table 2 support the catalytic participation of Cu in the formation of heterocycle **5n**. Furthermore, the thioester **6** could not be detected by GC-MS analysis even at a short reaction time, suggesting that the acetyl group migration would occur in a concerted manner with the addition of the nucleophilic sulfur atom to the imine carbon atom, (Scheme 2).

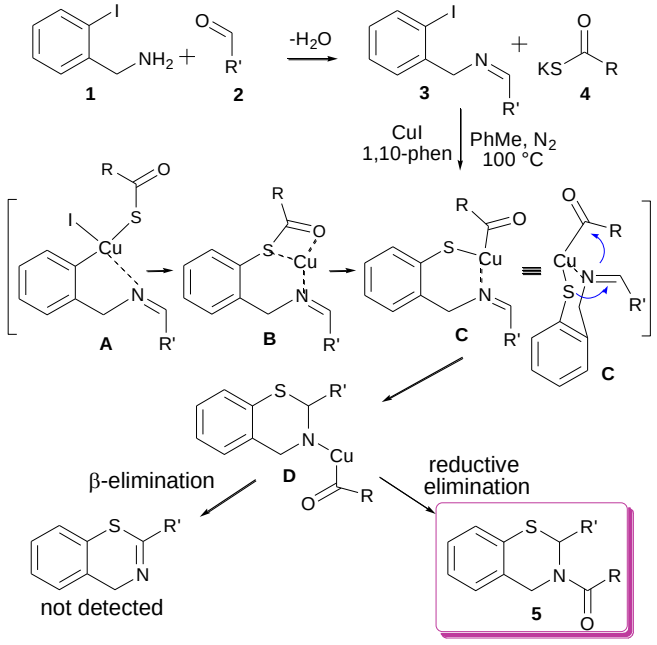
View Article Online DOI: 10.1039/C7QO00776G

TABLE 2. Cu-catalysed reaction of imine **3n** with potassium thioacetate (**4**).[a]



Entry	Cu/L[b]	Time (h)	**5n**, yield (%)[c]
1	CuI/1,10-phen	48	72 (89)
2	CuI/1,10-phen	24	49 (61)
3[d]	CuI/1,10-phen	24	0
4	1,10-phen	24	0
5	CuI	24	(19)
6[e]	CuI/1,10-phen	48	n.r.

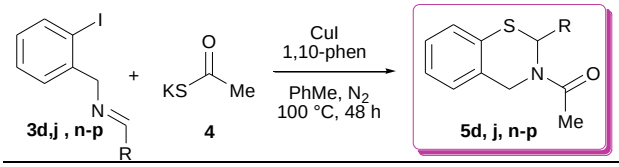
[a]Reaction Conditions: **3n** (0.5 mmol), **4** (1.5 equiv., 0.75 mmol) in toluene (4 mL) at 100 °C. [b]CuI (10 mol%, 0.05 mmol), 1,10-phenanthroline (20 mol%, 0.1 mmol). [c]Isolated yield and quantified by GC by the internal standard method between parentheses. [d]Under air atmosphere. [e]*N*-benzyl-1-phenylmethanimine instead of **3n** was used; n.r.: no reaction.

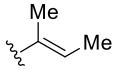


Scheme 2. Mechanistic proposal for the formation of 3,4-dihydro-2-phenyl-2*H*-benzo[*e*][1,3]thiazine (**5**).

To compare both procedures, different *N*-(2-iodobenzyl)-imine derivatives were synthesised by condensation of (2-iodophenyl) methanamine (**1**) with a set of aldehydes **2** and further isolated according to established methodologies. The limitation of this procedure involves low reactivity and therefore partial conversion of aldehydes substituted with EDGs, making imine isolation cumbersome. Indeed, **5f** could not be prepared by the two-step methodology due the impossible *p*-methoxy benzaldehyde-derived imine purification. Then, previously obtained imines were subjected to optimized reaction conditions (Table 2, entry 1) for the sequential synthesis of 3,4-dihydro-2*H*-benzo[*e*][1,3]thiazine (**5**), as depicted in Table 3.

TABLE 3. One-pot synthesis of 3,4-dihydro-2*H*-benzo[*e*][1,3]thiazines (**5d, j, n-p**) from imines (**3d, j, n-p**).[a]



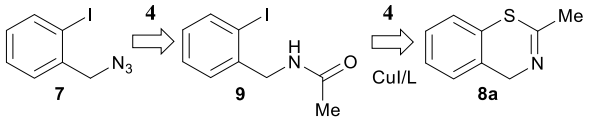
Entry	R	**5**, isolated yield (%)
1	Ph (**3n**)	**5n**, 72 (89)[b]
2	2-pyridyl (**3o**)	**5o**, 78
3[c]	2-pyridyl (**3o**)	**5o**, 46
4	*p*-CNC_6H_4 (**3d**)	**5d**, 86
5	*o*-$CF_3C_6H_4$ (**3j**)	**5j**, 23
6	 (**3p**)	**5p**, 79

[a]Reaction Conditions: **3** (0.5 mmol), **4** (1.5 equiv., 0.75 mmol), CuI (10 mol%, 0.05 mmol), 1,10-phenanthroline (20 mol%, 0.1 mmol) in toluene (4 mL) at 100 °C for 48 h. [b]Quantified by GC by the internal standard. [c]In the absence of ligand 1,10-phenanthroline.

The coupling of thioacetate with imino-derivatives bearing EWGs proceeded in good to excellent yields (Table 3, entries 2 and 4). The catalysed C-S coupling reaction of imine **3l** (which bears structural resemblance to known ligands)[27] was tested in the absence of any ancillary ligand, and moderate product yield was obtained (entry 3). When imine **3j** possessing a bulky EWG group in *ortho* position related to the imino functionality was employed, heterocycle **5j** was obtained in only 23% isolated yield (entry 5). These results indicate a noticeable steric effect of the CF_3 group[25] in the stepwise reaction in line with the observed for the one-pot procedure. Conversely, the reaction was carried out efficiently with imine **3p**, which derived from an aliphatic aldehyde. The use of this imine in the reaction produced the target heterocycle **5p** in excellent isolated yields (entry 6).

For the sake of comparison, heterocycle **5d** was obtained by both procedures. The one-pot reaction with 4-formylbenzonitrile afforded 60 % yield of **5d** from the corresponding aldehyde (Table 1, entry 4). Although a lower yield is obtained in comparison with the two-step methodology (Table 3, entry 4, 86%), the one-pot strategy comprises an additional reaction (imine formation) and avoids the imine intermediate purification step. Indeed, this performance is comparable to that obtained through the stepwise methodology for the synthesis of **5d**, starting from **1** and 4-formylbenzonitrile (first stage: imine **3d** obtained in 62% yield; second stage: **5d** obtained in 86% yield, global yield: 53%).Thus, the one-pot strategy is highly efficient, as it comprises three consecutive reactions (condensation to form an imine, Cu-catalysed C-S coupling and cyclisation), and allows access to novel heterocyclic structures.

Encouraged by the obtained results, we envisioned a cascade process departing from the *ortho*-iodobenzyl azide derivative, in which the azido group will give rise to an acetamido moiety upon reaction with thioacetate anion[28] and further reductive cyclisation with the *ortho*-thiolate installed by Cu-catalysed C-S coupling (Scheme 3).

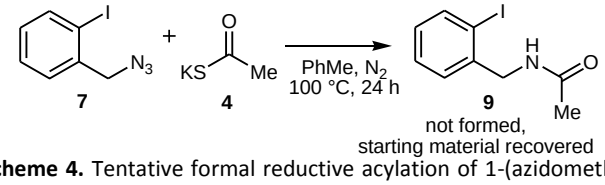


Scheme 3. Possible strategy to obtain 2-substituted 4*H*-benzo[*e*][1,3]thiazine (**8**) from 1-(azidomethyl)-2-iodobenzene (**7**).

Hence, we tested 1-(azidomethyl)-2-iodobenzene (**7**) as substrate in the Cu-catalysed reaction with **4**. Interestingly, this cascade strategy featuring the reaction of azide **7** with KSCOMe rendered heterocycle 2-methyl-4*H*-benzo[*e*][1,3]thiazine (**8a**) in good isolated yield (68 %), after 24 h of reaction (Table 4, entry 1).

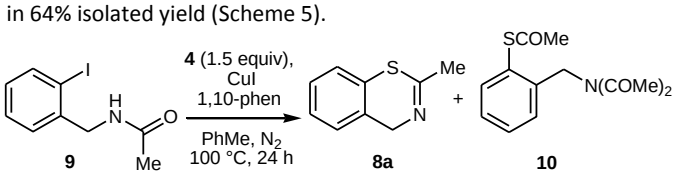
Next, other commercially available thiocarboxylic nucleophiles were evaluated in this cascade process. First, thiobenzoic acid was used and heterocycle 2-phenyl-4*H*-benzo[*e*][1,3]thiazine (**8b**) was obtained in 60 % yield (Table 4, entry 2). However, when potassium ethyl xanthogenate was tested as a nucleophile, lower yield of the expected heterocycle was obtained (36 % of **8c**, Table 4, entry 3), in agreement with previously reported works.[29] Substitution on the aryl azide moiety was also studied. Thus, the *p*-F substituted **7b** gave good yield of the benzothiazine **8d**, while the o-Me substituted **7c** afforded the thiol **11** (Table 4, entries 4 and 5).

In order to gain mechanistic insight, we performed two control experiments. In the first one, azide **7** was incubated with **4** (1.1 equiv.) in toluene under N_2 atmosphere, either in the presence or in the absence of a proton source ($KHCO_3$), the expected *o*-iodobenzylacetamide (**9**) was not formed in any case (Scheme 4).



Scheme 4. Tentative formal reductive acylation of 1-(azidomethyl)-2-iodobenzene (**7**).

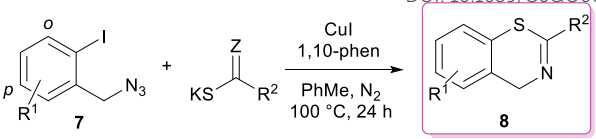
In addition, independently synthesised *N*-(2-iodobenzyl)acetamide (**9**) was subjected to Cu-catalysed C-S coupling with **4** under the same conditions, and 2-methyl-4*H*-benzo[*e*][1,3]thiazine (**8a**) was not detected. Instead, *S*-(2-((*N*-acetylacetamido)methyl)phenyl) ethanethioate (**10**) was obtained in 64% isolated yield (Scheme 5).

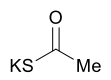
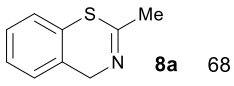
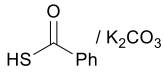
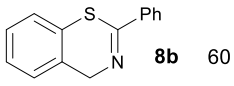
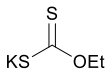
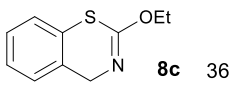
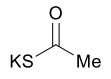
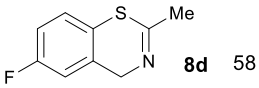
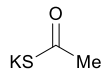
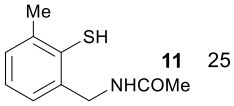


Scheme 5. Cu-catalyzed C-S coupling using *N*-(2-iodobenzyl)acetamide (**9**) as substrate.

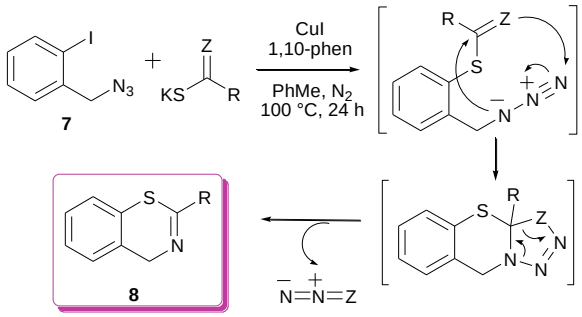
These results allow ruling out the participation of **9** in the reaction. A possible mechanism to account for the formation of heterocycles **8**, would involve a [3 + 2] dipolar cycloaddition yielding a five membered cyclic intermediate 1,2,3,4-thia(oxa)triazole derivative, which after extrusion of either sulfur dinitrogen (N_2S) or oxygen dinitrogen (N_2O) affords the corresponding benzothiazine **8** (Scheme 6).[30,31]

TABLE 4. One-pot synthesis of 4*H*-benzo[*e*][1,3]thiazines (**8a-d**) from azide **7**.[a]



Entry	R^1	Nucleophile	**8**, isolated yield (%)
1	**7a**, H		 **8a** 68
2[b]	**7a**, H		 **8b** 60
3	**7a**, H		 **8c** 36
4	**7b**, *p*-F		 **8d** 58
5	**7c**, *o*-Me		 **11** 25

[a]Reaction Conditions: **7** (0.25 mmol), nucleophile (1.5 equiv., 0.375 mmol), CuI (10 mol%, 0.025 mmol), 1,10-phenanthroline (20 mol%, 0.05mmol) in toluene (2 mL) at 100 °C for 24 h. [b]1.5 equiv. of K_2CO_3 were added.



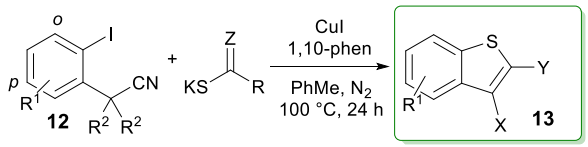
Scheme 6. Possible Mechanism for the formation of 2-substituted 4*H*-benzo[*e*][1,3]thiazine (**8**) from azide **7**.

Very recently, the Cu-catalysed benzo[*b*]thiophene synthesis from *o*-halophenylacetonitrile and (hetero)aromatic dithioesters was reported.[32] The reactions took place in DMF at 80 °C in the presence of 2 equiv. of K_3PO_4, 1.5 equiv. of pivalic acid and 20 mol% of CuI. So, we challenged our Cu-based methodology employing thiocarboxylic nucleophiles towards *o*-halophenylacetonitrile.

Thus, we selected 2-(2-iodophenyl)acetonitrile (**12**, R^1 = H) as an electrophile, which reacted with KSCOMe under Cu-catalysis affording 65 % isolated yield of *N*-(benzo[*b*]thiophen-2-yl)acetamide (**13a**, Table 5, entry 1).

Indeed, 2-aminobenzo[*b*]thiophene was previously synthesized from **12** by using Pd-catalysis and $Na_2S_2O_3$ as a sulfur source.[33] In this case, acetylation of the amine group could not be achieved during the reaction; instead, *N,N*-dimethylated product was obtained at expenses of the solvent (DMF).

TABLE 5. Selected examples for the synthesis of benzo[*b*]thiophenes from **12** and thiocarboxylic nucleophiles.[a]

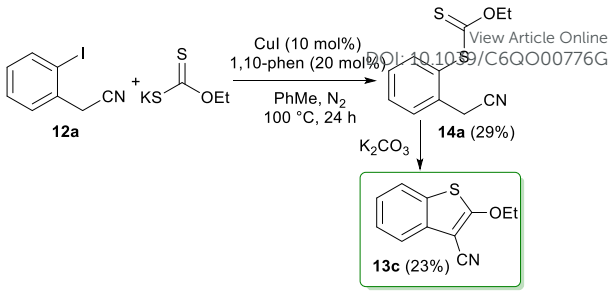


Entry	R^1	R^2	Nucleophile/base	**13**, isolated yields (%)
1 **12a**	H	H	KS, Me	**13a**, 65
2 **12a**	H	H	HS, Ph / K_2CO_3 1.5 eq	**13b**,45
3[b] **12a**	H	H	KS, OEt	**13c**, 0; **14a**, 29
4 **12b**	*p*-F	H	KS, Me	**13d**, 90
5 **12c**	*p*-Br	H	KS, Me	**13e**, 70
6 **12d**	*o*-Me	H	KS, Me	**13f**, 22
7 **12e**	H	Me	KS, Me	**13g**, 60
8 **12e**	H	Me	HS, Ph / K_2CO_3 1.5 eq	**13h**, 84

[a]Reaction Conditions: **12** (0.25 mmol), sulfur nucleophile (1.5 equiv., 0.375 mmol), CuI (10 mol%, 0.025 mmol), 1,10-phenanthroline (20 mol%, 0.05 mmol) in toluene (2 mL) at 100 °C for 24 h. Base = eq. of K_2CO_3 added. [b]Upon treatment with K_2CO_3, *S*-(2-(cyanomethyl)phenyl) *O*-ethyl carbonodithioate (**14a**) afforded 2-ethoxybenzothiophene-3-carbonitrile (**13c**) in 23 % isolated yield.

When thiobenzoic acid was used, 45% yield of the benzo[*b*]thiophene derivative **13b** was isolated (entry 2). However, the use of ethyl xanthogenate as a nucleophile did not produce the desired benzothiophene, instead, *S*-(2-(cyanomethyl)phenyl) *O*-ethyl carbonodithioate (**14a**) was obtained in 29 % isolated yield as a single product (Table 5, entry 3) (Scheme 7). When **14a** was treated with K_2CO_3, 2-ethoxybenzothiophene-3-carbonitrile (**13c**) was obtained, suggesting that benzylic deprotonation followed by addition to the carbonyl of the thioxanthate took place to render the stable benzothiophene.

p-Substitution on the aryl ring afforded good yields of **13d,e**, but



Scheme 7. Synthesis of 2-ethoxybenzothiophene-3-carbonitrile (**12c**) by reaction with ethyl xanthogenate.

the *ortho*-substituted iodide gave only 22% yield of **13f** (Table 4, entries 4-6).

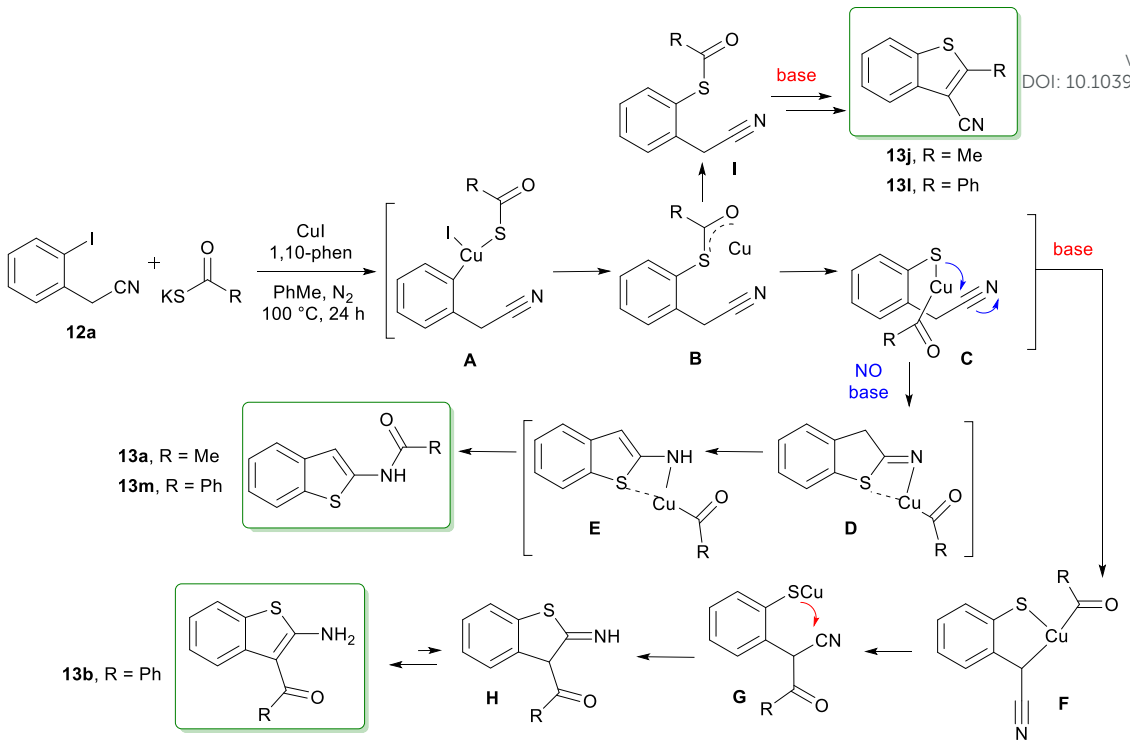
Once hydrogens at benzylic position were replaced by methyl groups (**12**, R^2 = Me), reaction of this substrate with either nucleophile (KSCOMe or HSCOPh/base), addition to the cyano group and *N*-acylation occurred with formation of the 3,3-dimethylbenzo[*b*]thiophene-2(3*H*)-imine derivatives **13g** and **13h** in 60 and 84 % isolated yields, respectively (entries 7 and 8).

Some control experiments, were performed using 2-phenylacetonitrile to evaluate the possibility of benzoylation or acetylation at the benzylic position with HSCOPh or KSCOMe, respectively in the presence of base and the catalytic systems of CuI and 1,10-phenanthroline, and, as expected, 2-phenylacetonitrile was recovered. These results confirm that C-S coupling is necessary for further rearrangements. When the reaction between **12** and KSCOMe is performed in the presence of 1.5 equiv of K_2CO_3, it afforded 22% yield of **13a** and the *N*-(3-acetylbenzo[*b*]thiophen-2-yl)acetamide (**13i**) in 37% yield (Table S1, entry 1, S.I.), while in the presence of 2.2 equiv of base, besides diacylated **13i** (19 %), 2-methylbenzo[*b*]thiophene-3-carbonitrile (**13j**) and diarylsulfide were obtained in 14 % and 40 % yield, respectively (Table S1, entry 2).

By using 3 equiv. of base in the reaction of HSCOPh with **12**, a mixture of **13b** (10%), dibenzoyl derivative **13k** (26%) and 3-cyano-2-phenylbenzothiophene **13l** (12%) was obtained (Table S1, entry 3). In the absence of base, as expected the reaction conversion is lower than 20 % affording *N*-(benzo[*b*]thiophen-2-yl)benzamide (**13m**) and *S*-2-(cyanomethyl)phenyl benzothioate (**14b**) in 10% and 4% isolated yield, respectively (Table S1, entry 4).

Based on the obtained results a putative mechanism can be proposed as follows (Scheme 8): the thiocarboxylate nucleophile displaces one 1,10-phenanthroline ligand from the initial CuL_2 complex, then an oxidative addition between the iodo atom and the aromatic carbon atom takes place to deliver intermediate **A**. The latter undergoes a reductive elimination to form thioester **B**, which coordinates the Cu(I). A second oxidative addition between the sulfur atom and the carbonyl of thioester functionality lead to Cu(III) intermediate **C**, in a similar fashion as described for Pd-catalysed Fukuyama coupling of thioesters and organozinc compounds.[34] Intermediate **C** can evolve differently depending on the presence of a base able to deprotonate the benzylic position readily activated by the cyano group. If base is present, the formed α–cyanocarbanion coordinates the Cu(III) centre that upon reductive elimination gives rise to the Cu(I) arenethiolate **G**. The latter features an α–cyano ketone motif that may suffer an

View Article Online
DOI: 10.1039/C6QO00776G



Scheme 8. Possible Mechanism involved in formation of 2-substituted benzo[*b*]thiophene derivatives.

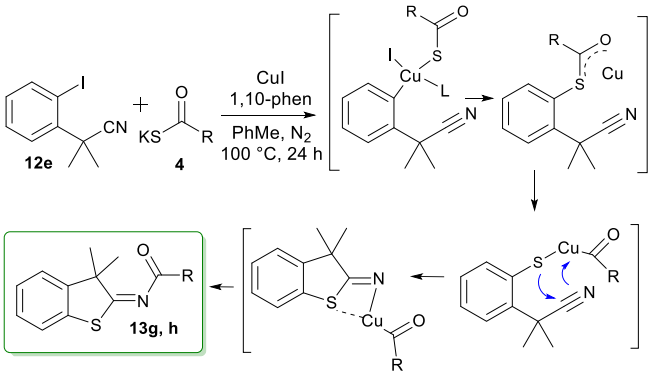
intramolecular nucleophilic attack of the Cu-thiolate moiety onto the electrophilic nitrile carbon,[35] thus rendering the 2-imino dihydrobenzo[*b*]thiophene **H**, which finally tautomerise to the aromatic 2-aminobenzo[*b*]thiophene product. Besides, depending on the reaction conditions, the 2-amino group can be benzoylated or acetylated by the thioesters affording **13i** or **13k**, respectively.[8a]

Meanwhile, in the absence of base, intermediate **C** evolves to the acyl Cu(III)-imino intermediate **D** through thiolate addition to the nitrile group. The latter aromatise thus forming **E**, that after reductive elimination furnish 2-(*N*-acyl)-aminobenzo[*b*]thiophene product.

As a general trend, after C-S coupling in the absence of base, only [S→N] acyl migration is attained. On the contrary, when additional base is used, both [S→C] and [S→N] acyl migration take place. This behaviour suggests that once the sulfur attacks the cyano group, the transiently formed imine or its tautomer is acylated, possibly in a concerted fashion by the action of a Cu-acyl complex.

Finally, in the presence of an excess of base it was possible to observe the intramolecular condensation 3-cyanobenzothiophene products (**13j** and **13l**) from the thioester coupling product **I**. In general, under these basic conditions, the different possible reaction channels effectively compete, including C-S bond cleavage of the thioester affording de diarylsulfide by a second Cu-catalysed coupling reaction.

In case the active benzylic position was blocked, [S→N] acyl migration is attained affording **13g** and **13h** regardless the presence or absence of base, even though no aromatisation can take place in the thiacycle. This observation suggests that driving force involved in this case is other than aromatisation. (Scheme 9).



Scheme 9. Possible Mechanism involved in formation of 2-acyliminodihydrobenzo[*b*]thiophene derivatives (**13g, h**).

It seems likely that the proposed mechanism for benzo[*b*]thiophene formation does not apply when ethyl xanthogenate is used as nucleophile. The oxidative addition of Cu(I) between sulfur and thiocarbonyl moiety appears to be impaired as compared with its thioester counterpart (Scheme 8, intermediate **C**), so, the C-S coupling product **14a** is obtained. Furthermore, the diaryl sulfide product from C-S cleavage of xanthogenate **14a** followed by a second Cu-catalysed cross coupling is observed along with **14a** in the presence of base (Table S1, entry 5).

Conclusions

In summary, we have developed two synthetic alternatives for obtaining six-membered sulfur heterocycles in cascade fashion. This practical and versatile methodology involves C–S bond formation by Cu-catalysis and followed by cyclisation process. This strategy allows obtaining in good yields either

DOI: 10.1039/C6QO00776G

3,4-dihydro-2*H*-benzo[*e*][1,3]thiazines or 4*H*-benzo[*e*][1,3] thiazines, selectively, by using properly substituted aryl iodides precursors.

For 3,4-dihydro-2*H*-benzo[*e*][1,3]thiazines (**5**), a simple one-pot procedure from amine **1** and aldehydes **2**, could be developed, thus avoiding the step of the imine isolation. This allows access to a variety of novel structures. The use of the corresponding imine as substrate rendered the expected products in good yields as well.

Besides, 4*H*-benzo[*e*][1,3] thiazines (**8**) could be easily achieved from 1-(azidomethyl)-2-iodobenzene (**7**) by reaction with thiocarboxylic nucleophiles.

Finally, a set of benzo[*b*]thiophene-related compounds (**13**) could be divergently obtained by using a nitrile derivative **12** as a starting electrophile and different thiocarboxylic nucleophiles. This work demonstrates that a general Cu-based catalytic system can be adopted for the preparation of several thiacyclic scaffolds.

Acknowledgements

This work was supported partly by Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) and Fondo de Ciencia y Tecnología (FONCYT), Argentina. S. M. S-C. gratefully acknowledges the receipt of a fellowship from CONICET.

Notes and references

1 H. Iino, T. Usui and J-I. Hanna, *Nat. Commun*. 2015, **6**, 6828.
2 A. J. Eberhart, H. Shrives, Y. Zhang, A. Carrër, A. V. S. Parry, D. J. Tate, M. L. Turner and D. J. Procter, *Chem. Sci.* 2016, **7**, 1281.
3 L. Fodor, G. Bernáth, J. Sinkkonen and K. Pihlaja, *J. Heterocycl. Chem.* 2002, **39**, 927.
4 T. Mizuhara, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem.* 2010, **75**, 265.
5 F. Benedini, G. Bertolini, F. Ferrario, R. Guindani and A. Sala, *J. Heterocycl. Chem.* 1994, **31**, 1589.
6 D. Jacob and H. Meier, *J. Heterocycl. Chem.* 1986, **23**, 1085.
7 I. P. Beletskaya and V. P. Ananikov, *Chem. Rev*. 2011, **111**, 1596.
8 a) S. M. Soria-Castro and A. B. Peñéñory, *Beilstein J. Org. Chem.* 2013, **9**, 467; b) V. K. Akkilagunta and R. R. Kakulapati, *J. Org. Chem.* 2011, **76**, 6819; c) F. Ke, X. Qu, Z. Jiang, Z. Li, D. Wu and K. Zhou, *Org. Lett,* 2011, **13**, 454; d) H-J. Xu, X-Y. Zhao, J. Deng, Y. Fu and Y-S. Feng, *Tetrahedron Lett.* 2009, **50**, 434; e) F. Y. Kwong and S. L. Buchwald, *Org. Lett.* 2002, **4**, 3517; f) C. G. Bates, R. K. Gujadhur and D. Venkataraman, *Org. Lett.* 2002, **4**, 2803.
9 H. Liu and X. Jiang, *Chem. Asian J.* 2013, **8**, 2546.
10 For selected examples see: a) B. Luo, Q. Cui, H. Luo, Y. Hu, P. Huang and S. Wen, *Adv. Synth. Catal.* 2016, **358**, 2733; b) A. S. Reddy and K. C. K. Swamy, *Org. Lett.* 2015, **17**, 2996; c) D. Ma, Q. Geng, H. Zhang and Y. Jiang, *Angew. Chem. Int. Ed.* 2010, **49**, 1291; d) H. Deng, Z. Li, F. Ke and X. Zhou, *Chem. Eur. J.* 2012, **18**, 4840; e) N. Park, Y. Heo, M. R. Kumar, Y. Kim, K. H. Song and S. Lee, *Eur. J. Org. Chem.* 2012, 1984; f) A. R. Rosario, K. K. Casola, C. E. S. Oliveira and G. Zeni, *Adv. Synth. Catal.* 2013, **355**, 2960.
11 a) A. Senthilvelan and V. T. Ramakrishnan, *Tetrahedron Lett.* 2002, **43**, 5119; b) A. Senthilvelan, D. Thirumalai and V. T. Ramakrishnan, *Tetrahedron* 2004, **60**, 851.
12 a) M. Schmidt, H. Meier, S. A. Saleh, *J. Heterocycl. Chem.* **1991**, *28*, 573; b) D. Gröschl, H.-P. Niedermann, H. Meier, *Chem. Ber.* **1994**, *127*, 955.
13 A. Herrera, R. Martínez-Alvarez, P. Ramiro, A. Sánchez and R. Torres, *J. Org. Chem.* 2004, **69**, 4545.
14 F. Lach, *Synlett* 2012, **23**, 2639.
15 S. E. Denmark and A. Thorarensen, *Chem. Rev.* 1996, **96**, 137.
16 D. Chen, J. Wu, J. Yang, L. Huang, Y. Xiang and W. Bao, *Tetrahedron Lett.* 2012, **53**, 7104.
17 S. Dadiboyena, *Eur. J.Med. Chem.* 2012, **51**, 17.
18 a) C. D. Jones, M. G. Jevniker, A. J. Pike, M. K. Peters, L. J. Black, A. R. Thompson, J. F. Falcone and J. A. Clemens, *J. Med. Chem.* 1984, **27**, 1057; b) Z. Wang, W. Geng, H. Wang, S. Zhang, W.-X. Zhang and Z. Xi, *Tetrahedron Lett.* 2011, **52**, 6997.
19 M. V.Patel, J. J. Rohde, V. Gracias and T. Kolasa, *Tetrahedron Lett.* 2003, **44**, 6665.
20 A.V. Kalinin, M.A. Reed, B.H. Norman and V. Snieckus, *J. Org. Chem.* 2003, **68**, 5992.
21 B. Gabriele, R. Mancuso, E. Lupinacci, L. Veltri, G. Salerno and C. Carfagna, *J. Org. Chem.* 2011, **76**, 8277.
22 For selected examples using Pd, see: a) M. C. Willis, D. Taylor and A. T. Gillmore, *Tetrahedron* 2006, **62**, 11513; b) C.S. Bryan, J. A. Braunger and M. Lautens, *Angew. Chem. Int. Ed.* 2009, **48**, 7064; using Cu, see: c) C. Wang, L.-L. Sun, B.-L. Hu, X.-G. Zhang and F. Chen, *Tetrahedron* 2014, **70**, 7969; d) L.-L. Sun, C.-L. Deng, R.-Y. Tang and X.-G. Zhang, *J. Org. Chem.* 2011, **76**, 7546; e) H. Yu, M. Zhang and Y. Li, *J. Org. Chem.* 2013, **78**, 8898.
23 S. M. Soria-Castro, *Synlett* 2012, **23**, 2997.
24 F. T. Edelmann, *Comments Inorg. Chem.* 1992, **12**, 259.
25 a) M. B. Smith and J. March, *March´s Advances Organic Chemistry, 6th ed.* John Wiley & Sons, New Jersey, 2007, pp. 411; b) A. Dumitrescu, V. L. Rudzevich, V. D. Romanenko, A. Mari, W. W. Schoeller, D. Bourissou and G. Bertrand, *Inorg. Chem.* 2004, **43**, 6546.
26 a) B. Zou, Q. Yuan and D. Ma, *Angew. Chem. Int. Ed.* 2007, **46**, 2598; b) X. Liu, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem. Int. Ed.* 2009, **48**, 348; c) D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong and Y. Jiang, *Angew. Chem. Int. Ed.* 2009, **48**, 4222.
27 a) H.-J. Cristau, P. P. Cellier, J.-F. Spindler and M. Taillefer, *Chem. Eur. J.* 2004, **10**, 5607; b) A. Ouali, J.-F. Spindler, H.-J. Cristau and M. Taillefer, *Adv. Synth. Catal.* 2006, **348**, 499; c) A. Ouali, J.-F. Spindler, A. Jutand and M. Taillefer, *Adv. Synth. Catal.* 2007, **349**, 1906.
28 a) N. Shangguan, S. Katukojvala, R. Greenberg and L. J. Williams, *J. Am. Chem. Soc.* 2003, **125**, 7754; b) H. Paulsen, T. Bielfeldt, S. Peters, M. Meldal and K. Bock, *Liebigs Ann. Chem.* 1994, 369.
29 Higher reactivity of ethyl xanthogenate has been observed when polar solvents (DMF and DMSO) and BINAM as ligand were used, while only low reactivity displayed in nonpolar solvents, such as toluene, used in the present work. See: a) D. J. C. Prasad and G. Sekar, *Org. Lett.* 2011, **13**, 1008; b) S. Sangeetha, P. Muthupandi and G. Sekar, *Org. Lett.* 2015, **17**, 6006.
30 Formation of N_2S was demonstrated in the thermolysis of 5-phenyloxy-1,2,3,4-thiatriazole. See: a) C. Wentrup and P. Kambouris, *Chem. Rev.* 1991, **91**, 363; b) C. Wentrup and R. Flamang, *J. Phys. Org. Chem.* 1998, **11**, 350.
31 Episulfidation of strained cycloalkenes by thermolysis of 5-aryloxy-1,2,3,4-thiatriazoles suggest the *in situ* formation of N_2S. See: W. Adam and R. M. Wargon, *Eur. J. Org. Chem.* 2001, 1959.
32 N. C. Sandhya, K. N. Nandeesh, K. S. Rangappa and S. Ananda, *RSC Adv.* 2015, **5**, 29939.
33 C. Hou, Q. He and C. Yang, *Org. Lett.* 2014, **16**, 5040.
34 a) R. Oost, A. Misale and N. Maulide, *Angew. Chem. Int. Ed.* 2016, **55**, 4587; b) L. S. Liebeskind and J. Srogl, *J. Am. Chem. Soc.* 2000, **122**, 11260.
S. Kim and J. I. Lee, *J. Chem. Soc. Chem. Comm*. 1981, 1231.

View Article Online
DOI: 10.1039/C6QO00776G

Journal Name

ARTICLE