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Copper-Catalysed Cascade Synthesis of Imidazolidine–Benzothiazole and Imidazolidine–Tetrazole Hybrid Heterocycles from Bis-thioureas by a Desulfurisation Strategy

Ganesh Majji,[a][‡] Santosh K. Sahoo,[a][‡] Nilufa Khatun,[a] and Bhisma K. Patel*[a]

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The in situ generated bis-thioureas obtained by treating aryl/alkyl isothiocyanates with aliphatic 1,2-diamines, upon treatment with Cu^{I} or Cu^{II} salts, depending on their quantity and the reaction conditions, furnished either imidazolidine-carbothioamide (ImCAT) or imidazolidine–benzothiazole (ImBT) hybrid molecules. The same reactions in the presence of sodium azide yielded imidazolidine–tetrazoles (ImTets). The products were obtained in good yields at room temperature with all these processes taking place in a single pot. This is a perfect illustration of Cu salts serving as both desulfurising as well as C–H activating agents at ambient temperature.

Introduction

The transformation of simple precursors into a diverse array of multifunctional molecules in one pot is of paramount interest to both academic and industrial research. Thiophilic reagents such as diacetoxyiodobenzene (DIB), bromine or its equivalent 1,1′-(ethane-1,2-diyl)dipyridinium bis(tribromide) (EDPBT) have been reported to give various N, O and S heterocycles and key organic intermediates such as isothiocyanates, cyanamides and carbodiimides by a desulfurisation strategy using substituted thioureas or its analogues.[1] Other thiophilic reagents such as iodine also serve as an equally efficient desulfurising agent giving carbodiimides from 1,3-disubstituted thioureas[2a] and organic cyanamides from alkyl/aryl thioamides.[2b,2c] The above-mentioned reagents are required in stoichiometric amounts to achieve the desired transformations. In recent years, transition-metal-catalysed tandem reactions have led to the construction of heterocycles, polycycles and natural products.[3] Among these reactions, copper-catalysed protocols have emerged as vital tools in the synthesis of a wide variety of heterocyclic frameworks.[4] As a part of our ongoing research into Cu-catalysed processes, our group and others have contributed a number of one-pot protocols for the synthesis of various biologically important N, O and S heterocycles.[5] Recently, we demonstrated that a catalytic quantity of a Cu salt in the presence of a base can efficiently desulfurise arylthioureas to aryl cyanamides.[6a] The ability of Cu salts to act as efficient desulfurising agents was also revealed during the synthesis of amino-substituted tetrazoles, triazoles, oxadiazoles and thiadiazoles by the oxidative desulfurisation of their respective thiourea precursors.[6b] Besides these, there are two other examples of copper-catalysed oxidative desulfurisation of thioamides and their subsequent transformations.[7] A unique example of an amidic oxygen functioning as a nucleophile in a Cu-catalysed oxidative coupling of an imine C–H bond in the synthesis of 2,5-disubstituted [1,3,4]oxadiazole has been demonstrated by us.[8] Although copper-catalysed intermolecular thiolation by C–H activation are well documented in the literature,[9] the selective formation of C–S bonds has been little reported. This is because of the catalyst poisoning caused by sulfur compounds and the tendency of thioamidic substrates towards oxidative dimerisation and oxidation to amides.[7a,10]

Recently, hybrid molecules have gained remarkable importance in drugs discovery and other biological applications. Benzothiazoles are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and the treatment of diabetes,[11a] epilepsy,[11b–11d] inflammation,[12a] amyotrophic lateral sclerosis,[12b] analgesia,[12c] tuberculosis[12d] and viral infections.[12e] Similarly, imidazoline-containing molecules exhibit a considerable array of biological activities.[13] Thus, combining these two important pharmacophoric units, namely imidazolidine and benzothiazole, would be useful from the point of view of pharmaceutical properties. Taking cues from the desulfurising[1,2,6,7] and C–H activating ability[5h,8,9] of Cu catalysts, the construction of a hybrid molecule possessing an imidazolidine and a benzothiazole pharmacophore can be envisaged from bis-thioureas derived from aryl/alkyl isothiocya-

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[a] Department of Chemistry, Indian Institute of Technology Guwahati,
Guwahati 781039, Assam, India
E-mail: patel@iitg.ernet.in
http://www.iitg.ac.in/patel/

[‡] Both authors have contributed equally to this paper.

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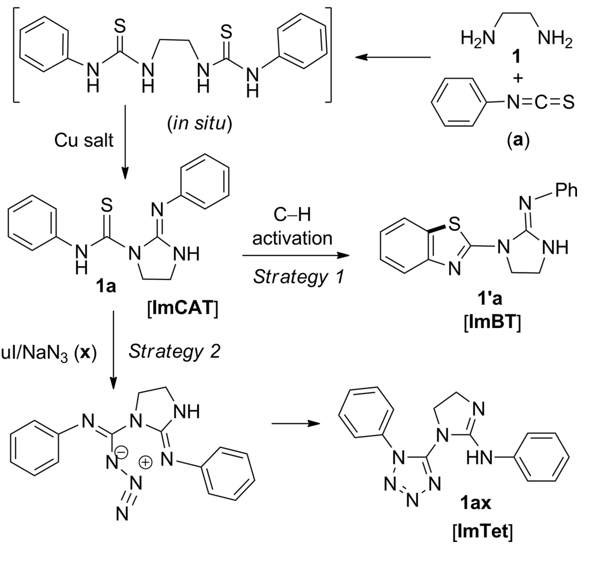
nates and aliphatic 1,2-diamines. If copper behaves as a thiophilic/desulfurising agent similarly to other thiophilic reagents such as DIB or iodine, the bis-thiourea would yield imidazolidinecarbothioamide (ImCAT) **1a**, as shown in Scheme 1. So far there are four methods reported in the literature for the synthesis of imidazolidinecarbothioamide **1a**. The two classical methods for its synthesis involve the desulfurisation of bis-thioureas using a toxic mercuric salt[14] or the treatment of 2-methylamino-2-imidazoline with an isothiocyanate.[15] Recently, our group developed two greener approaches, one using a slightly expensive reagent, diacetoxyiodobenzene (DIB),[1a] and the other using an unconventional bis(tribromide) reagent, 1,1′-(ethane-1,2-diyl)dipyridinium bis(tribromide) (EDPBT).[1b] Because Cu shows intramolecular as well as intermolecular C–H activation potential, the formation of benzothiazole by a C–H activation path to give imidazolidine–benzothiazole (ImBT) **1′a** cannot be ruled out (Scheme 1, *Strategy 1*). Alternatively, if the thiophilic power of Cu prevails, it may activate the sulfur towards an intramolecular electrophilic substitution reaction to form the benzothiazole skeleton, thus giving the hybrid molecule imidazolidine–benzothiazole **1′a**, as shown in Scheme 1 (Strategy 1). In fact, by using a stoichiometric amount of various copper salts, the corresponding imidazolidine–copper complexes have been isolated.[5h]



Scheme 1. Possible reaction path for the formation of ImCAT, ImBT and ImTet.

On the other hand, there are only two instances in which imidazolidine–tetrazole hybrid molecules have proven useful, one in medicinal applications and the other in organocatalysis.[16–20] The derivative 5-(4-benzyl-1-methylimidazolidin-2-yl)-1*H*-tetrazole has been used as an organocatalyst in the asymmetric conjugate addition of nitroalkanes.[20e] Thus, the development of efficient strategies for the synthesis of tetrazole derivatives is attractive due to their potential myriad of applications. Traditional methods for the synthesis of tetrazoles include the treatment of secondary amides or thioamides with $TMSN_3/Et_3N/Hg^{II}$, PCl_5/HN_3 or $TMSN_3/Ph_3P/DEAD$.[21] However, these methods require harsh reaction conditions, long reaction times, tedious work-up and the use of toxic metal salts. In recent years, the oxidative desulfurisation strategy has become an effective method for the synthesis of tetrazoles. An oxidative-desulfurisation-based protocol for the construction of tetrazoles has been achieved by using toxic thiophilic metals such as Pb and Hg salts.[22] In an attempt to avoid the use of toxic metals, two greener strategies, one by our group using molecular iodine[2d] and the other using hypervalent iodine,[23] have been developed. In addition, Cu salts in catalytic quantities have been found to be effective in the desulfurisation of thioureas, and this strategy has been successfully employed for the synthesis of various azoles possessing additional N, O and S atoms.[6b]

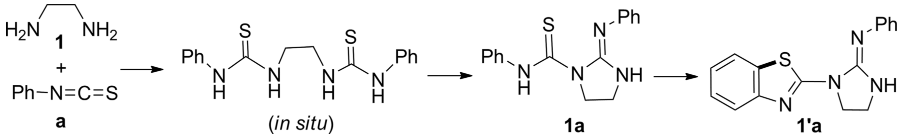
In all the above processes, various heterocycles have been constructed by the desulfurisation of thioureas/thioamides.[2d,5h,6b,22,23] As seen above, the mono-desulfurisation of bis-thioureas in the presence of copper salts gives imidazolidinecarbothioamides (ImCATs) in which one of the thioamidic (thiourea) units remains intact. A second desulfurisation of the ImCATs in the presence of an azido nucleophile would give intermediate azido-imidazolidine species that may undergo further intramolecular cycloaddition to provide imidazolidine–tetrazole hybrid heterocycles (Scheme 1).

Results and Discussion

To test the feasibility of our proposed strategy 1 (Scheme 1), the in situ generated thiourea obtained by treating phenyl isothiocyanate (**a**) and ethylenediamine (**1**) was treated with CuI (20 mol-%) and Na_2CO_3 (1 equiv.; Table 1, entry 1) in an ethanolic medium and the reaction mixture was stirred at room temperature under air. The thiophilic salt CuI was chosen because of our recent success with it during the catalytic synthesis of cyanamides from arylthioamides.[6] The reaction mixture, however, was found not to be so clean while monitoring by TLC; several N and S donor atoms present in the expected product may form a complex with the Cu salt.[5h] A control reaction was performed in the absence of a copper catalyst and any other additive, that is, by simply heating the bis-thiourea in ethanol at 80 °C; ImCAT was formed but in a yield of $<10\%$ after 15 h. To characterise the product (ligand), the metal-bound ligand was removed from the complex by treating the reaction mixture with an aqueous ammoniacal solution. The organic products were extracted with EtOAc and the major product, phenyl(phenylimino)imidazolidinecarbothioamide (**1a**), was isolated in 58% yield along with traces of imidazolidine–benzothiazole **1′a** (ImBT; ca. 5%).[5h] The formation of both these products (**1a** and **1′a**; Scheme 1) revealed that our strategy worked as expected. A decent conversion using a sub-stoichiometric amount of CuI suggests the catalytic nature of the reagent.

Initially, we optimised the reaction conditions so as to achieve exclusively the intermediate imidazolidinecarbothioamide (ImCAT) **1a** by using Cu^{II} salts as they are thio-

Table 1. Screening of the reaction conditions for the desulfurisation of bis-thioureas.



Entry	Catalyst (mol-%)	Base	Solvent	Time [h]	Temp. [°C]	Yield[a] [%]	
						1a	**1′a**
1	CuI (20)	Na_2CO_3	EtOH	12	25	58	5
2	CuCl (20)	Na_2CO_3	EtOH	12	25	61	3
3	$CuBr_2$ (20)	Na_2CO_3	EtOH	12	25	75	2
4	CuO (20)	Na_2CO_3	EtOH	12	25	38	n.d.
5	$Cu(OH)_2$ (20)	Na_2CO_3	EtOH	12	25	46	n.d.
6	$CuSO_4{\cdot}5H_2O$ (20)	Na_2CO_3	EtOH	12	25	68	5
7	$Cu(OAc)_2{\cdot}2H_2O$ (20)	Na_2CO_3	EtOH	12	25	69	5
8	$Cu(NO_3)_2{\cdot}3H_2O$ (20)	Na_2CO_3	EtOH	12	25	48	n.d.
9	$CuCl_2{\cdot}2H_2O$ (20)	Na_2CO_3	EtOH	12	25	85	3
10	$CuCl_2{\cdot}2H_2O$ (20)	K_2CO_3	EtOH	12	25	76	5
11	$CuCl_2{\cdot}2H_2O$ (20)	Et_3N	EtOH	12	25	69	3
12	$CuCl_2{\cdot}2H_2O$ (20)	Na_2CO_3	THF	12	25	56	n.d.
13	$CuCl_2{\cdot}2H_2O$ (20)	Na_2CO_3	DMSO	12	25	58	8
14	$CuCl_2{\cdot}2H_2O$ (20)	Na_2CO_3	MeOH	12	25	68	5
15	$CuCl_2{\cdot}2H_2O$ (20)	Na_2CO_3	MeCN	12	25	86	3
16	$CuCl_2{\cdot}2H_2O$ (30)	Na_2CO_3	EtOH	28	25	13	45
17	$CuCl_2{\cdot}2H_2O$ (40)	Na_2CO_3	EtOH	28	25	8	65
18	$CuCl_2{\cdot}2H_2O$ (50)	Na_2CO_3	MeCN	28	25	0	63
19	$CuCl_2{\cdot}2H_2O$ (40)	Na_2CO_3	MeCN	28	25	5	63

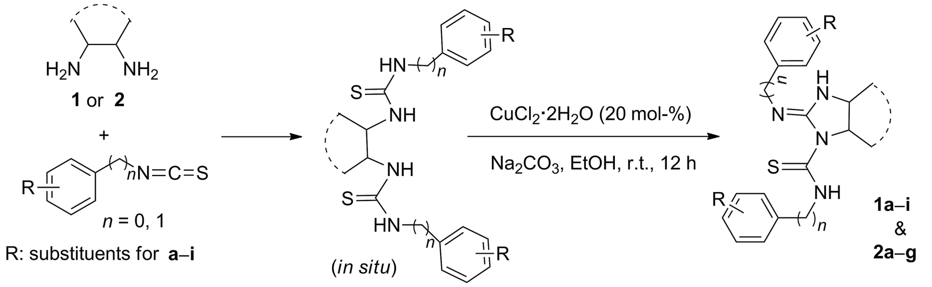
[a] n.d.: not detected.

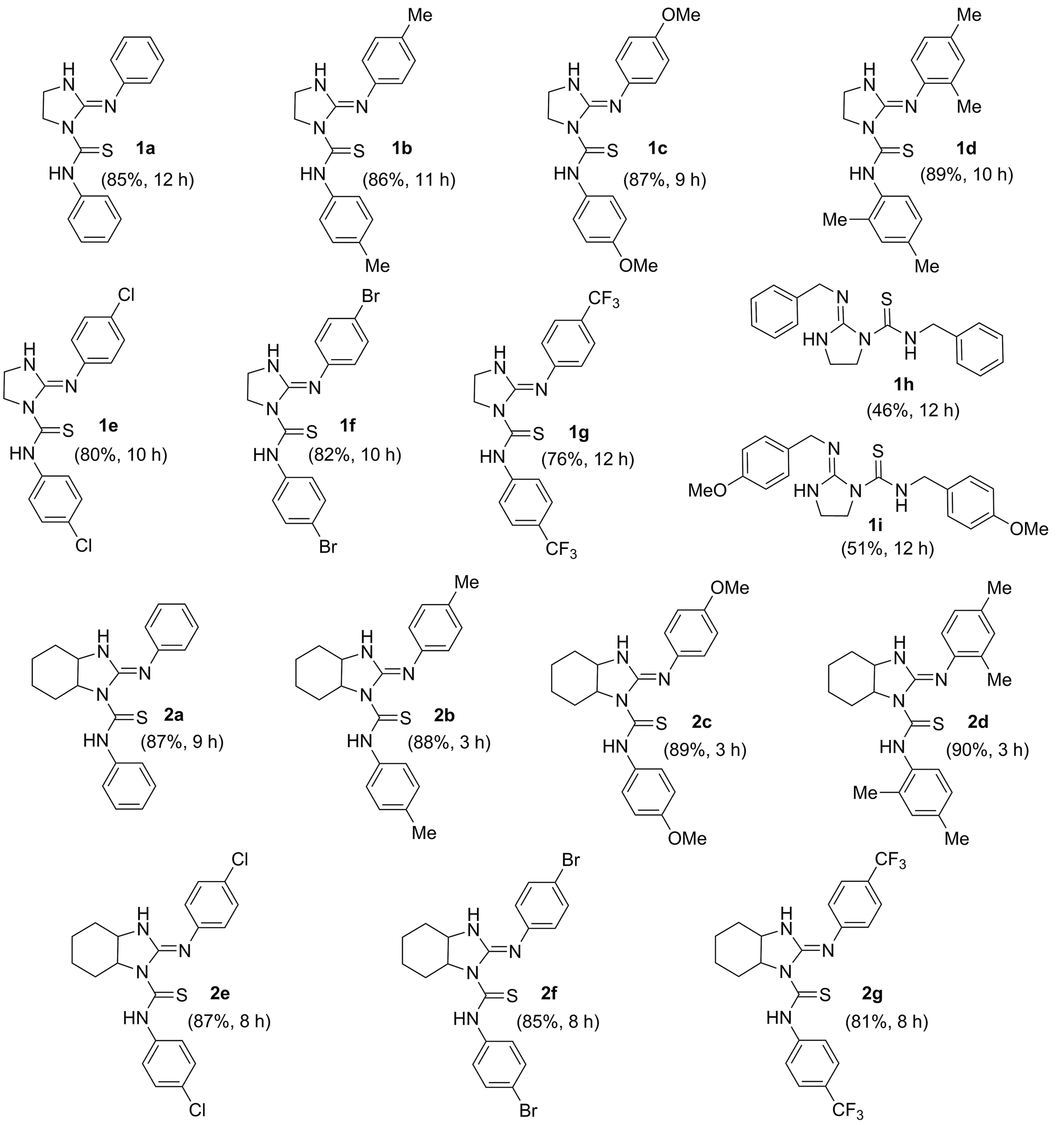
philic, inexpensive, environmentally benign and easy to handle. Of the monovalent (CuCl) and divalent copper salts [$CuBr_2$, CuO, $Cu(OH)_2$, $CuSO_4{\cdot}5H_2O$, $Cu(OAc)_2{\cdot}2H_2O$, $Cu(NO_3)_2{\cdot}3H_2O$ and $CuCl_2{\cdot}2H_2O$, Table 1, entries 2–9] tested, the dihydrated salt of $CuCl_2$ was found to be the best (Table 1, entry 9). Ethanol was preferred over other solvents such as MeOH, THF, DMSO and CH_3CN (Table 1, entries 9–15) as it gave a better yield as well as being environmental acceptable. The use of Na_2CO_3 (Table 1, entry 9) as base gave better results than other bases such as K_2CO_3 and Et_3N tested (Table 1, entries 10 and 11). Thus, solvent EtOH, catalyst $CuCl_2{\cdot}2H_2O$ and Na_2CO_3 as base gave an isolated yield of 85% of **1a** along with a trace (ca. 3%) of **1′a** at room temperature under air after 12 h (Table 1, entry 9).

Having optimised the reaction conditions, this strategy was then applied to other in situ generated bis-diarylthioureas derived from 1,2-ethylenediamine (**1**) and various aryl isothiocyanates (**a**–**g**) possessing electron-donating *p*-Me (**b**), *p*-OMe (**c**) and 2,4-di-Me (**d**), moderately electron-withdrawing *p*-Cl (**e**) and *p*-Br (**f**) as well as strongly electron-withdrawing *p*-CF_3 (**g**) groups in the aryl rings; imidazolidinecarbothioamide (ImCAT) products **1a**–**1g** were exclusively obtained, as shown in Table 2. Similarly, bis-dibenzylthioureas derived from 1,2-ethylenediamine (**1**) and benzyl isothiocyanates **h** and **i** gave the corresponding imidazolidinecarbothioamides **1h** and **1i**, but in relatively low yields (Table 2). The reaction of the cyclic aliphatic 1,2-diamine, *trans*-1,2-diaminocyclohexane (**2**), with aryl isothiocyanates bearing electron-donating *p*-Me (**b**), *p*-OMe (**c**) and 2,4-di-Me (**d**) groups gave good yields of their respective products **2b**–**2d**. Similarly, moderately electron-withdrawing *p*-Cl (**e**) and *p*-Br (**f**) as well as strongly electron-withdrawing *p*-CF_3 (**g**) groups in the aryl rings of isothiocyanate all gave excellent yields of their respective products **2e**–**2g**. It should be mentioned here that in general bis-thioureas derived from the rigid aliphatic cyclic 1,2-diamine (**2**) gave superior yields in shorter reaction times than the bis-thioureas derived from the conformationally flexible ethylenediamine (**1**; Table 2). Substrates possessing electron-donating substituents gave marginally better yields than substrates bearing electron-withdrawing groups (Table 2). The bis-thioureas derived from *o*-phenylenediamine and aryl isothiocyanates did not give the expected ImCAT products, rather they gave benzimidazoles along with the expulsion of the aryl isothiocyanate group, which is consistent with the results of our earlier work.[1a,1b]

In the above cases, imidazolidinecarbothioamides (ImCATs) were obtained as the major products (Table 2) along with traces of imidazolidine–benzothiazoles (ImBTs) (Table 1). When the reaction was prolonged, the yields of the imidazolidine–benzothiazoles (ImBTs) increased, and were probably formed by a C–H activation path.[5h] Note that there has not been a single report on the synthesis of hybrid heterocycle imidazolidine–benzothiazoles (ImBTs), except for some of their copper complexes,[5h] thus the reaction parameters were further optimised. The in situ generated thiourea obtained by treating phenyl isothiocyanate (**a**) and ethylenediamine (**1**) with 20 mol-% of $CuCl_2$ gave imidazolidinecarbothioamide **1a** (ImCAT) as the major product along with traces of ImBT **1′a** after 12 h. No substantial improvement in the yield of the latter product could be ob-

Table 2. One-pot synthesis of imidazolidinecarbothioamides (ImCATs) from aryl/alkyl isothiocyanates and 1,2-diamines.[a,b]



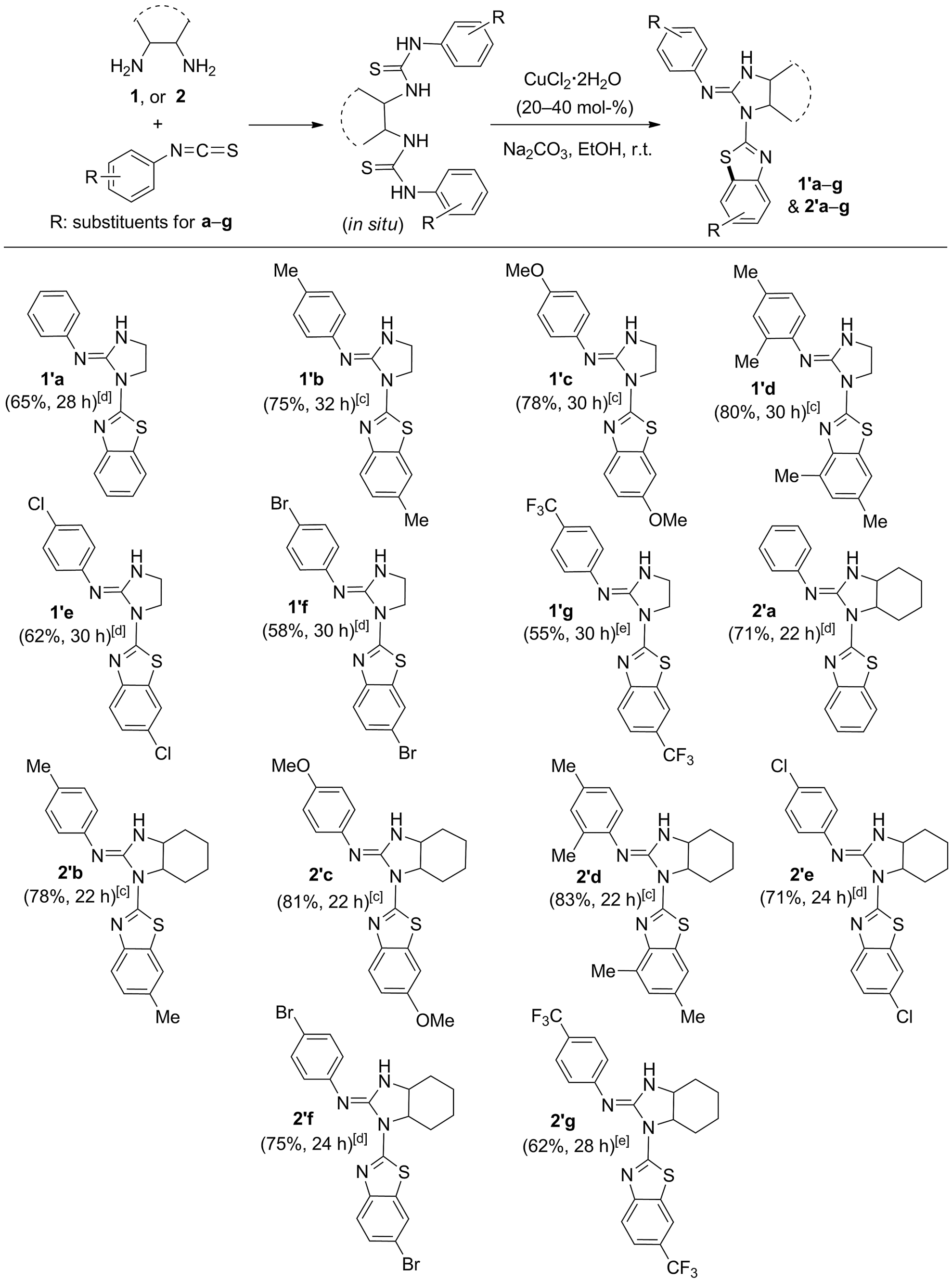


[a] Isolated yields are given. [b] The reactions were monitored by TLC and the products characterised by spectroscopic analysis.

served even after prolonging the reaction time to 48 h or by heating the reaction mixture. This is because the catalyst remained bound to ImBT in the form of a [Cu(ImBT)] complex.[5h]

However, upon increasing the quantity of the Cu salt to 40 mol-% and allowing the reaction to proceed for upto 28 h, the major product obtained upon aqueous ammoniacal work-up was found to be the imidazolidine–benzothiazole (ImBT) **1′a**. The details of further optimisations are shown in Table 1 (entries 16–19), and are very much substrate dependent, as is discussed below. It should be mentioned here that 40 mol-% of the catalyst ($CuCl_2·2H_2O$) is essential for the reactions of thioureas derived from aryl isothiocyanates possessing electron-withdrawing groups such as Cl (**e**) and Br (**f**), but for substrates possessing the electron-donating groups Me (**b**), OMe (**c**) and di-Me (**d**), the reaction proceeds efficiently with 20 mol-% of the catalyst. From these observations it is clear that in addition to the simple Cu salts, the [Cu(ImBT)] complexes[5h] also serve as efficient catalysts for this transformation, particularly for the C–H activation step (Scheme 1). Having optimised the reaction conditions, this strategy was then applied to other in situ generated bis-diarylthioureas derived from acyclic diamine **1** or cyclic 1,2-diamine **2** and various aryl isothiocyanates possessing electron-donating Me (**b**), OMe (**c**) and di-Me (**d**) and electron-withdrawing Cl (**e**) and Br (**f**) groups. All the in situ generated bis-diarylthioureas gave exclusively the corresponding imidazolidine–benzothiazoles (ImBTs) **1′a**–**1′f** and **2′a**–**2′f**, as shown in Table 3. For the aryl isothiocyanate possessing the strongly electron-withdrawing

Table 3. One-pot synthesis of imidazolidine–benzothiazoles (ImBTs) from aryl isothiocyanates and 1,2-diamines.[a,b]



[a] Isolated yields are given. [b] The reactions were monitored by TLC and the products characterised by spectroscopic analysis. [c] 20 mol-% of $CuCl_2 \cdot 2H_2O$ was used. [d] 40 mol-% of $CuCl_2 \cdot 2H_2O$ was used. [e] A stoichiometric amount of $CuCl_2 \cdot 2H_2O$ was used.

group p-CF_3 (**g**), a stoichiometric amount of $CuCl_2$ was essential to achieve the conversion to **1′g** and **2′g** in modest yields. For electron-poor substrates, a polar aprotic solvent such as acetonitrile was found to be better than the polar protic solvent ethanol. It is noteworthy that electron-rich substrates showed higher reactivity towards intramolecular C–H activation than substrates with electron-withdrawing groups in the aryl ring (Table 3). These results are consistent with the observations of Buchwald and Nagasawa and their co-workers for similar C–N and C–O bond-forming reactions.[24]

By using the conditions similar to those above and of our previous reports,[6b] we re-investigated the formation of imidazolidine–tetrazole (Strategy 2, Scheme 1). The treatment of phenyl isothiocyanate (**a**; 2 equiv.) with ethylenediamine (**1**; 1 equiv.) in DMSO at 80 °C furnished the corresponding bis-thiourea within 10 min. The in situ generated bis-thiourea provided *N*-phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (**1a**) on treatment with CuI (10 mol-%) and Cs_2CO_3 (2 equiv.) for 3 h, as shown in Table 2. NaN_3 (3 equiv.) was added to this reaction mixture and the reaction was allowed to continue for a further 4 h. The expected imidazolidine–tetrazole **1ax** was obtained in an isolated yield of 32%. Encouraged by this result, a series of optimisation reactions were performed to arrive at the maximum possible yield. The use of K_2CO_3 as base was found to be inferior (23%) and the organic base Et_3N gave an improved yield (40%). A further 8% improvement in the yield (48%) was observed when the solvent was replaced by DMF. Interestingly, when the reaction was performed at 60 °C, the product **1ax** was isolated in 60% yield. However, when the same reaction was carried out either at room temperature or below 50 °C the yield was severely affected, giving yields of around 26%. The lower yield at low temperature is a consequence of thermodynamic parameters, whereas the better yield at 60 °C is due to fewer competitive reaction pathways as compared with at the higher temperature of 80 °C. An increase in the quantity of the base Et_3N (3 equiv.) resulted in an improved yield (70%). However, the yield remained unaltered with further increases in the quantity of base. The yield of the product dropped with a decrease in the amount of sodium azide (2 equiv., 63%) or catalyst (5 mol-%, 42%). The use of other Cu salts as catalysts, such as $Cu(OAc)_2$ (58%), $CuCl_2$ (62%), $CuSO_4$ $5H_2O$ (45%), $CuBr_2$ (50%), CuCl (65%) and CuBr (63%), were slightly inferior compared with CuI (70%). Thus, the most favourable conditions for the formation of **1ax** are the use of CuI (10 mol-%), Et_3N (3 equiv.) and NaN_3 (3 equiv.) in DMF as solvent at 60 °C.

The optimised reaction conditions were then applied to the synthesis of a diverse array of imidazolidine–tetrazoles from the corresponding bis-thioureas. This methodology is compatible with a wide range of functional groups, tolerating both electron-donating and -withdrawing substituents. For example, bis-thioureas derived from 1,2-ethylenediamine (**1**) and aryl isothiocyanates possessing the electron-donating substituents p-Me and p-Bu gave the corresponding imidazolidine–tetrazoles **1bx** and **1hx**. The structure of the product **1bx** was confirmed by X-ray crystallographic analysis (Figure 1).[25] Similarly, bis-thioureas obtained from 1,2-ethylenediamine (**1**) and aryl isothiocyanates bearing the weakly deactivating substituents p-F, p-Cl, p-Br, p-I, m-Br and o-Br gave the corresponding imidazolidine–tetrazoles **1ix**, **1ex**, **1fx**, **1jx**, **1kx** and **1lx** hybrid heterocycles in excellent yields. The in situ generated 2,4-di-F- and p-CF_3-substituted bis-thioureas also gave the imidazolidine–tetrazoles **1mx** and **1gx** in yields of 63 and 83%, respectively. As can be seen from Table 4, the yields obtained are higher for substrates possessing electron-withdrawing groups than for substrates with electron-donating substituents. This trend in yields is consistent with the results of our earlier work in which tetrazole derivatives were synthesised from their mono-thiourea precursors.[6b] However, the in situ generated bis-thioureas derived from aryl isothiocyanates and 1,2-diaminocyclohexane (**2**) also furnished the corresponding hybrid heterocyclic scaffolds (**2ax**, **2bx**, **2ix**, **2fx** and **2kx**) in good yields. Here again, similar electronic effects of the substituents on the phenyl ring were observed, as reflected by their yields (Table 4).

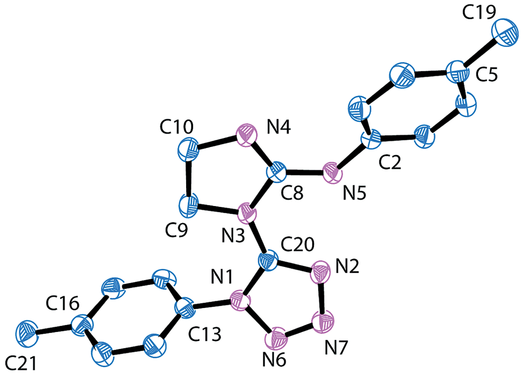
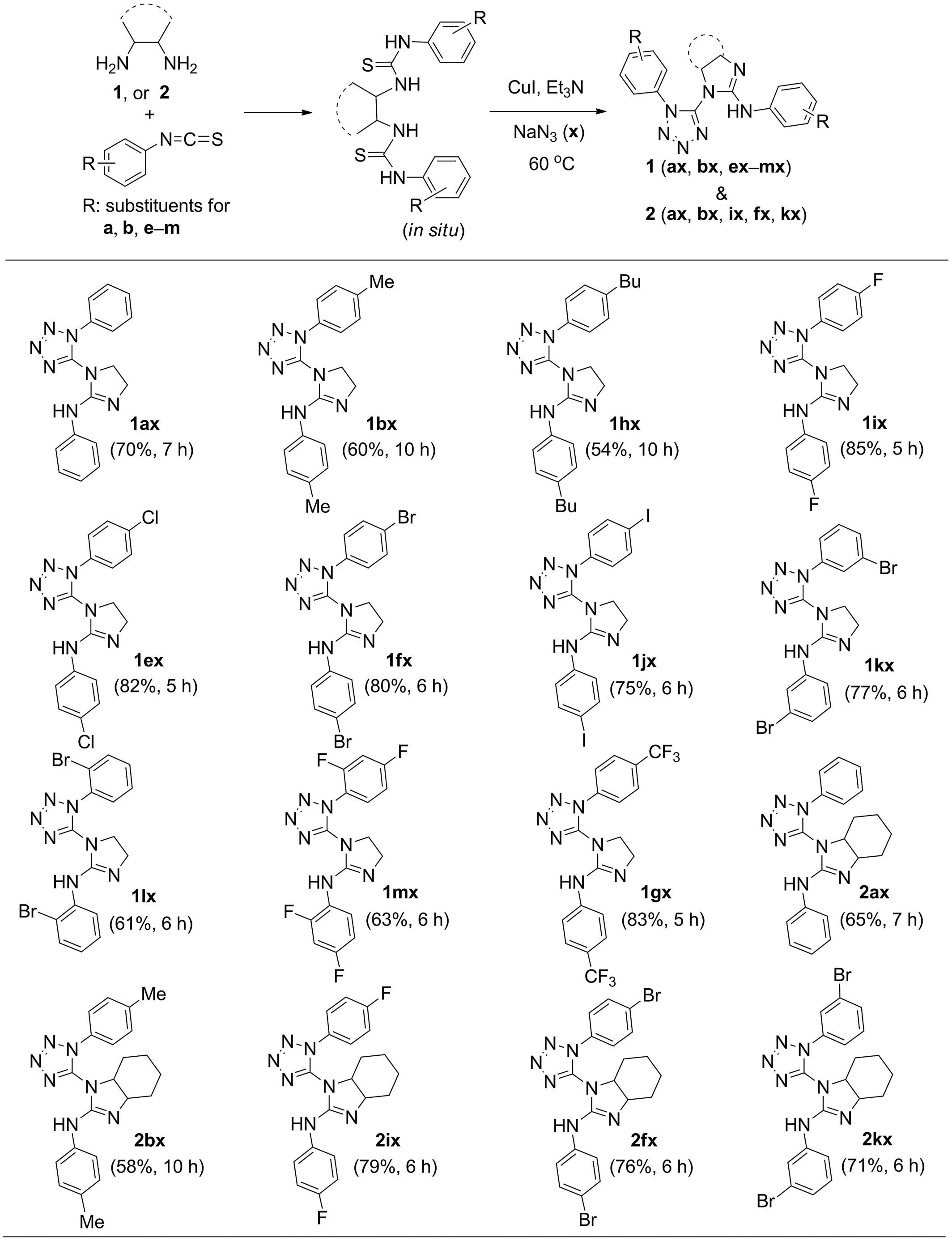


Figure 1. ORTEP molecular diagram of the structure of **1bx**.

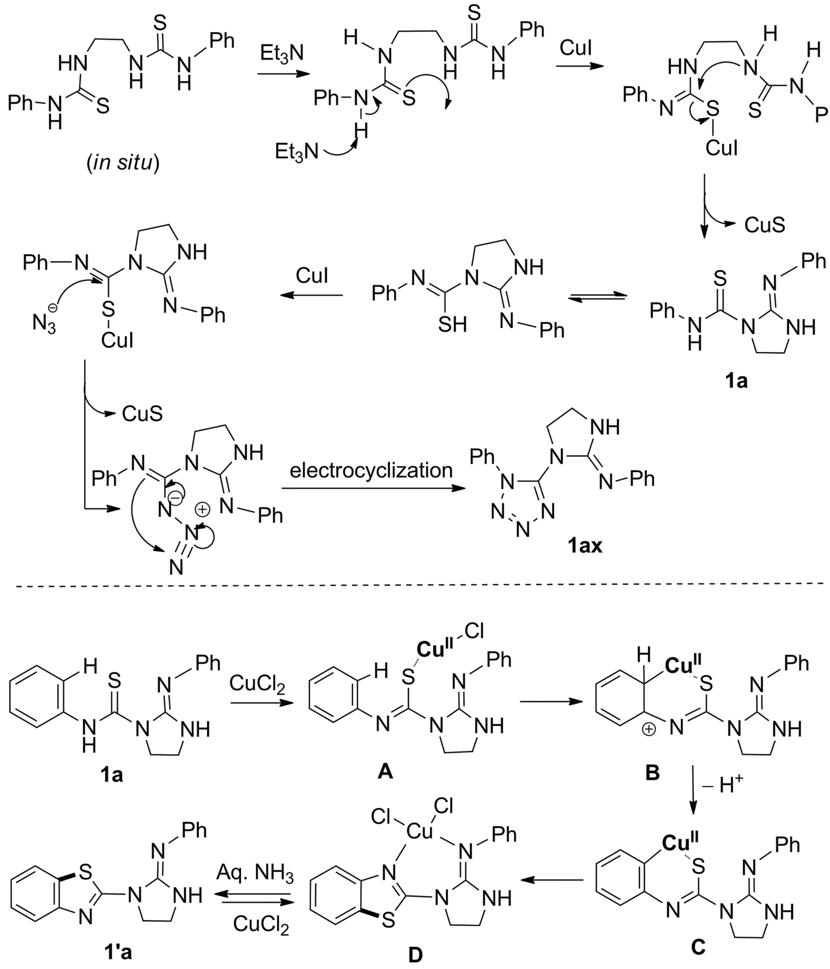
Based on literature reports[5h,6b] and control experiments, a plausible mechanism for the formation of the imidazolidine–tetrazoles is depicted in Scheme 2. One of the sulfur atoms in the bis-thiourea is activated by the thiophilic Cu salt. The imine carbon is then attack intramolecularly by one of the thioamidic nitrogen atoms with the expulsion of CuS to give imidazolidinecarbothioamide **1a**, as shown in Scheme 2. The formation of both CuS and **1a** was confirmed by their isolation and characterisation.[6b] Under the present reaction conditions, the in situ generated CuS is converted into CuO, as has been observed earlier by us.[6b] This in situ generated CuO is equally effective in bringing about a similar desulfurisation.[6b] The treatment of isolated imidazolidinecarbothioamide **1a** in the presence of NaN_3 under otherwise identical conditions gave product **1ax**. The second sulfur atom in imidazolidinecarbothioamide **1a** is activated by the thiophilic Cu salt and is attacked by the external nucleophile azide (N_3) to give an azido-imidazolid-

Table 4. Substrate scope for the synthesis of imidazolidine–tetrazoles by oxidative double desulfurisation.[a]



[a] The reactions were monitored by TLC and the products characterised by spectroscopic analysis. The yields of the isolated pure products are reported.

?ine species (Scheme 2). Intramolecular electrocyclisation of the azido-imidazolidine leads to the formation of the imidazolidine–tetrazole hybrid heterocycle **1ax**. Although we have not thoroughly investigated the reaction mechanism for the formation of the hybrid molecule **1′a** from **1a**, the reaction path could be analogous to the one that has been proposed for a similar C–N coupling reaction by Brasche and Buchwald[24a] or for a C–O coupling reaction by Nagasawa and co-workers[24b,24c] as well as our own (Scheme 2).[1a,1b,5h]



Scheme 2. Proposed mechanism for the formation of ImCAT, ImBT and ImTet.

Conclusions

The in situ generated bis-diarylthioureas derived from aliphatic 1,2-diamines and aryl/alkyl isothiocyanates undergo an efficient copper-catalysed cascade synthesis of imidazolidine–benzothiazoles (ImBTs). This is a unique demonstration of Cu salts serving both as a desulfurising as well as a C–H activating agent at ambient temperature. The double desulfurisation of bis-thiourea, catalysed by Cu^I, leads to the construction of imidazolidine–tetrazoles (ImTets) in a single operation. These hybrid heterocycles, which possess two important pharmacophoric units, may have potential applications in synthetic and pharmaceutical chemistry.

Experimental Section

General Procedure for the Preparation of (*E*)-*N*-Phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (1a) Using $CuCl_2·2H_2O$ as Catalyst: Ethylenediamine (**1**; 60 mg, 1 mmol) was added to a solution of phenyl isothiocyanate (**a**; 270 mg, 2 mmol) in EtOH (10 mL) and the reaction mixture was stirred at room temperature. The complete formation of bis-thiourea was observed within 20 min (monitored by TLC), and is associated with the formation of a white precipitate. Na_2CO_3 (1 mmol) and $CuCl_2·2H_2O$ (0.2 mmol) were added to this heterogeneous reaction mixture and the reaction mixture was stirred at room temperature under air. The progress of the reaction was monitored by TLC by taking small aliquots, diluting with ethyl acetate and treatment with a few drops of 30% aqueous ammonia. After shaking for 1 min, the aqueous layer turned blue and the product present in the ethyl acetate layer was spotted by TLC. After complete disappearance of the starting thiourea, ethanol was removed under reduced pressure and ethyl acetate (25 mL) was added followed by 30% aqueous ammonia (5 mL). The resulting biphasic layer was stirred for 5 min. The organic layer was then separated and dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product so obtained was purified over a short column of silica gel by using EtOAc/hexane (2:8) as eluent to give the product **1a** (260 mg, yield 85%). The identity and purity of the product was confirmed by spectroscopic analysis.

General Procedure for the Preparation of (*E*)-*N*-[1-(Benzo[*d*]thiazol-2-yl)imidazolin-2-ylidine]aniline (1′a) Using $CuCl_2·2H_2O$ as Catalyst: A procedure similar to that used for the synthesis of **1a** was adopted except 0.4 mmol of $CuCl_2·2H_2O$ was used instead of 0.2 mmol; yield 191 mg (65%).

General Procedure for the Preparation of *N*-Phenyl-1-(1-phenyl-1*H*-tetrazol-5-yl)-4,5-dihydro-1*H*-imidazol-2-amine (1ax) Using CuI as Catalyst: A mixture of 1,2-ethylenediamine (**1**; 60 mg, 1 mmol) and phenyl isothiocyanate (**a**; 270 mg, 2 mmol) in DMF (2 mL) was stirred in a pre-heated oil bath at 60 °C for 10 min. After the complete formation of 1,1′-(ethane-1,2-diyl)bis(3-phenylthiourea), as judged by TLC, CuI (19 mg, 0.1 mmol) and Et$_3$N (303 mg, 3 mmol) were added to the reaction mixture under air. The disappearance of the in situ generated thiourea and appearance of a new spot having a higher R_f were observed within 3 h. NaN$_3$ (**x**; 195 mg, 3 mmol) was added to this reaction mixture and stirred for a further 4 h. During this period, the progress of the reaction was monitored by TLC. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (10 mL). Then the reaction mixture was filtered through a bed of Celite and washed with ethyl acetate (20 mL). The combined filtrate was washed with water (3 × 5 mL). The ethyl acetate layer was dried with anhydrous Na$_2$SO$_4$ and the solvent removed under reduced pressure. The crude product was purified over a column of silica gel and eluted with hexane/ethyl acetate (7:3) to give *N*-phenyl-1-(1-phenyl-1*H*-tetrazol-5-yl)-4,5-dihydro-1*H*-imidazol-2-amine (**1ax**; 213 mg, 70% yield).

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[1] a) H. Ghosh, R. Yella, J. Nath, B. K. Patel, *Eur. J. Org. Chem.* **2008**, 6189; b) R. Yella, B. K. Patel, *J. Comb. Chem.* **2010**, *12*, 754; c) H. Ghosh, R. Yella, A. R. Ali, S. K. Sahoo, B. K. Patel, *Tetrahedron Lett.* **2009**, *50*, 2407; d) R. Yella, H. Ghosh, S. Murru, S. K. Sahoo, B. K. Patel, *Synth. Commun.* **2010**, *40*, 2083; e) C. B. Singh, H. Ghosh, S. Murru, B. K. Patel, *J. Org. Chem.* **2008**, *73*, 2924; f) R. Yella, V. Kavala, B. K. Patel, *Synth. Commun.* **2011**, *41*, 792; g) S. K. Sahoo, N. Khatun, H. Jena, B. K. Patel, *Inorg. Chem.* **2012**, *51*, 10800; h) H. Ghosh, B. K. Patel, *Org. Biomol. Chem.* **2010**, *8*, 384; i) J. Nath, H. Ghosh, R. Yella, B. K. Patel, *Eur. J. Org. Chem.* **2009**, 1849.

[2] a) A. R. Ali, H. Ghosh, B. K. Patel, *Tetrahedron Lett.* **2010**, *51*, 1019; b) J. Nath, B. K. Patel, L. Jamir, U. Bora, K. V. V. V. Satyanarayana, *Green Chem.* **2009**, *11*, 1503; c) J. Nath, L. Jamir, B. K. Patel, *Green Chem. Lett. Rev.* **2011**, *4*, 1; d) R. Yella, N. Khatun, S. K. Rout, B. K. Patel, *Org. Biomol. Chem.* **2011**, *9*, 3235.

[3] a) R. A. A. Foster, M. C. Willis, *Chem. Soc. Rev.* **2013**, *42*, 63; b) H. Pellissier, *Chem. Rev.* **2013**, *113*, 442; c) J. Yu, F. Shi, L.-Z. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156.

[4] a) M. Carril, R. SanMartin, E. Dominguez, *Chem. Soc. Rev.* **2008**, *37*, 639; b) S. R. Chemler, P. H. Fuller, *Chem. Soc. Rev.* **2007**, *36*, 1153; c) J. Sheng, B. Chao, H. Chen, Y. Hu, *Org. Lett.* **2013**, *15*, 4508; d) S. Guo, J. Wang, X. Fan, X. Zhang, D. Guo, *J. Org. Chem.* **2013**, *78*, 3262; e) B. Gabriele, L. Veltri, P. Plastina, R. Mancuso, M. V. Vetere, V. Maltese, *J. Org. Chem.* **2013**, *78*, 4919; f) Z.-M. Chen, W. Bai, S.-H. Wang, B.-M. Yang, Y.-Q. Tu, F.-M. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 9781.

[5] a) A. Banerjee, S. K. Santra, S. K. Rout, B. K. Patel, *Tetrahedron* **2013**, *69*, 9096; b) N. Khatun, L. Jamir, M. Ganesh, B. K. Patel, *RSC Adv.* **2012**, *2*, 11557; c) S. K. Sahoo, N. Khatun, A. Gogoi, A. Deb, B. K. Patel, *RSC Adv.* **2013**, *3*, 438; d) S. K. Rout, S. Guin, J. Nath, B. K. Patel, *Green Chem.* **2012**, *14*, 2491; e) S. Murru, P. Mondal, R. Yella, B. K. Patel, *Eur. J. Org. Chem.* **2009**, 5406; f) S. Murru, B. K. Patel, J. L. Bras, J. Muzart, *J. Org. Chem.* **2009**, *74*, 2217; g) S. Murru, H. Ghosh, S. K. Sahoo, B. K. Patel, *Org. Lett.* **2009**, *11*, 4254; h) S. K. Sahoo, H. S. Jena, G. Majji, B. K. Patel, *Synthesis* **2014**, *46*, 1886; i) K. Inamoto, C. Hasegawa, K. Hiroya, T. Doi, *Org. Lett.* **2008**, *10*, 5147; j) P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul, T. Punniyamurthy, *J. Org. Chem.* **2009**, *74*, 8719; k) D. Cauzzi, G. Predieri, A. Tiripicchio, R. Zanoni, C. Giori, *Inorg. Chim. Acta* **1994**, *221*, 183.

[6] a) S. K. Sahoo, L. Jamir, S. Guin, B. K. Patel, *Adv. Synth. Catal.* **2010**, *352*, 2538; b) S. Guin, S. K. Rout, A. Gogoi, S. Nandi, K. K. Ghara, B. K. Patel, *Adv. Synth. Catal.* **2012**, *354*, 2757.

[7] a) F. Shibahara, A. Suenami, A. Yoshida, T. Murai, *Chem. Commun.* **2007**, 2354; b) F. Shibara, A. Yoshida, T. Murai, *Chem. Lett.* **2008**, *37*, 646.

[8] S. Guin, T. Ghosh, S. K. Rout, A. Banerjee, B. K. Patel, *Org. Lett.* **2011**, *13*, 5976.

[9] a) S. Zhang, P. Qian, M. Zhang, M. Hu, J. Cheng, *J. Org. Chem.* **2010**, *75*, 6732; b) L. Chu, X. Yue, F.-L. Qing, *Org. Lett.* **2010**, *12*, 1645; c) S. Ranjit, R. Lee, D. Heryadi, C. Shen, J. Wu, P. Zhang, K.-W. Huang, X. Liu, *J. Org. Chem.* **2011**, *76*, 8999; d) A.-X. Zhou, X.-Y. Liu, K. Yang, S.-C. Zhao, Y.-M. Liang, *Org. Biomol. Chem.* **2011**, *9*, 5456.

[10] a) L. L. Hegedus, R. W. McCabe, *Catalyst Poisoning*, Marcel Dekker, New York, **1984**; b) K. Inamoto, C. Hasegawa, J. Kawasaki, K. Hiroya, T. Doi, *Adv. Synth. Catal.* **2010**, *352*, 2643.

[11] a) H. Suter, H. Zutter, *Helv. Chim. Acta* **1967**, *50*, 1084; b) S. J. Hays, M. J. Rice, D. F. Ortwine, G. Johnson, R. D. Schwartz, D. K. Boyd, L. F. Copeland, M. G. Vartanian, P. A. Boxer, *J. Pharm. Sci.* **1994**, *83*, 1425; c) P. Jimonet, F. Audiau, M. Barreau, J.-C. Blanchard, A. Boireau, Y. Bour, M.-A. Coleno, A. Doble, G. Doerflinger, C. Do Huu, M.-H. Donat, J. M. Duchesne, P. Ganil, C. Gueremy, E. Honore, B. Just, R. Kerphirique, S. Gontier, P. Hubert, P. M. Laduron, J. Le Blevec, M. Meunier, J.-M. Miquet, C. Nemecek, M. Pasquet, O. Piot, J. Pratt, J. Rataud, M. Reibaud, J.-M. Stutzmann, S. Mignani, *J. Med. Chem.* **1999**, *42*, 2828; d) Y. He, A. Benz, T. Fu, M. Wang, D. F. Covey, C. F. Zorumski, S. Mennick, *Neuropharmacology* **2002**, *42*, 199.

[12] a) S. N. Sawhney, S. K. Arora, J. V. Singh, O. P. Bansal, S. P. Singh, *Indian J. Chem.* **1978**, *16B*, 605; b) G. Bensimon, L. Lacomblez, V. Meininger, *New Engl. J. Med.* **1994**, *330*, 585; c) G. Foscolos, G. Tsatsas, A. Champagnac, M. Pommier, *Ann. Pharm. Fr.* **1977**, *35*, 295; d) V. G. Shirke, A. S. Bobade, R. P. Bhamaria, B. G. Khadse, S. R. Sengupta, *Indian Drugs* **1990**, *27*, 350; e) C. J. Paget, K. Kisner, R. L. Stone, D. C. Delong, *J. Med. Chem.* **1969**, *12*, 1016.

[13] a) L. Heys, C. G. Moore, P. J. Murphy, *Chem. Soc. Rev.* **2000**, *29*, 57; b) D. Laeckmann, F. Rogister, J.-V. Dejardin, C. Prosperi-Meys, J. Geczy, J. Delarge, B. Masereel, *Bioorg. Med. Chem.* **2002**, *10*, 1793; c) D. Castagnolo, S. Schenone, M. Botta, *Chem. Rev.* **2011**, *111*, 5247.

[14] R. Walter, O. Reudiger, *Chem. Ber.* **1973**, *106*, 484.

[15] D. Wilfried, B. Peter, S. H. Joachim, L. Klaus, R. R. Schmidt, EU Pat. App. No. EP 451651, **1991**.

[16] M. Fujinaga, T. Yamasaki, J. Yui, A. Hatori, L. Xie, K. Kawamura, C. Asagawa, K. Kumata, Y. Yoshida, M. Ogawa, N. Nengaki, T. Fukumura, M.-R. Zhang, *J. Med. Chem.* **2012**, *55*, 2342.

[17] M. Gutschow, M. Schlenk, J. Gab, M. Paskaleva, M. W. Alnouri, S. Scolari, J. Iqbal, C. E. Muller, *J. Med. Chem.* **2012**, *55*, 3331.

[18] F. Curreli, S. Choudhury, I. Pyatkin, V. P. Zagorodnikov, A. K. Bulay, A. Altieri, Y. D. Kwon, P. D. Kwong, A. K. Debnath, *J. Med. Chem.* **2012**, *55*, 4764.

[19] M. S. Sa, D. Pla, M. Altuna, A. Francesch, C. Cuevas, F. Albericio, M. Alvarez, *J. Med. Chem.* **2009**, *52*, 6217.

[20] a) H. A. Al-Tamamy, M. E. A. Fattah, *Orient. J. Chem.* **2010**, *26*, 421; b) D. Moderhack, B. Holtmann, *J. Prakt. Chem.* **2000**, *342*, 591; c) D. Moderhack, D.-O. Bode, D. Schomburg, *Chem. Ber.* **1993**, *126*, 129; d) G. L'Abbé, M. Gelinne, S. Toppet, *J. Heterocycl. Chem.* **1989**, *26*, 729; e) A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897.

[21] M. Spulak, R. Lubojacky, P. Senel, J. Kunes, M. Pour, *J. Org. Chem.* **2010**, *75*, 241, and references cited therein.

[22] a) W. G. Finnegan, R. A. Henry, E. Lieber, *J. Org. Chem.* **1953**, *18*, 779; b) R. A. Batey, D. A. Powell, *Org. Lett.* **2000**, *2*, 3237.
[23] P. S. Chaudhari, S. P. Pathare, K. G. Akamanchi, *J. Org. Chem.* **2012**, *77*, 3716.
[24] a) G. Brasche, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 1932; *Angew. Chem.* **2008**, *120*, 1958; b) S. Ueda, H. Nagasawa, *Angew. Chem. Int. Ed.* **2008**, *47*, 6411; *Angew. Chem.* **2008**, *120*, 6511; c) S. Ueda, H. Nagasawa, *J. Org. Chem.* **2009**, *74*, 4272.
[25] CCDC-1063526 (for **1bx**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See also the Supporting Information.

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