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Isothiocyanation of Amines Using Langlois Reagent

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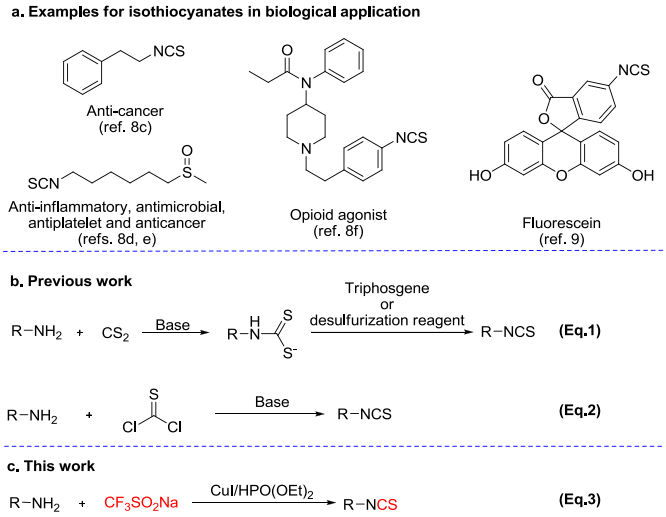
Langlois reagent was found to be effective for the isothiocyanation of primary amines in the presence of copper iodide and diethyl phosphonate.

The Langlois reagent (F_3CSO_2Na) is an intriguing trifluoromethylating agent that has been widely used for the preparation of numerous useful trifluoromethylated molecules.[1-4] In recent years, F_3CSO_2Na has also been employed as a trifluoromethylthiolating and trifluoromethanesulfonylating agent in organic synthesis.[5] Among the various studies concerning the synthetic application of F_3CSO_2Na, early reports demonstrated that thiocarbonyl fluoride could be obtained from the deoxygenative reduction of F_3CSO_2Na.[6] We envisaged that the *in situ* formed thiocarbonyl fluoride could be trapped and stabilized by amines to produce isothiocyanates. Isothiocyanates are promising antimicrobial candidates and pharmaceutically active compounds (Scheme 1a).[7,8] Additionally, isothiocyanates have also been used as organic dyes for the labelling of immunoglobulins in biosystems (Scheme 1a).[9] The significant biological activity of isothiocyanates prompted us to develop a novel method for isothiocyanation with good functional group tolerance. Traditional synthetic methods for the preparation of isothiocyanates involve the use of CS_2, phosgene or thiophosgene, reagents which are all highly toxic (Scheme 1b, Eqs. 1 and 2).[10-13] Although these protocols have proven to be effective for the isothiocyanation of a number of aromatic amines, the high toxicity of phosgenes and thiophosgenes remains a serious problem. In order to mitigate these problems and develop a more environmentally benign[14] synthesis of isothiocyanates, the use of the inexpensive and stable F_3CSO_2Na as an isothiocyanating reagent is highly desirable. Herein, we report a copper-catalyzed isothiocyanation of amines using the Langlois reagent in the presence of diethyl phosphonate (Scheme 1c, Eq.3).



Scheme 1 Biological application and synthetic methods of isothiocyanates.

In order to develop optimal reaction conditions for the isothiocyanation reaction, initial studies began with the reaction of ethyl 4-aminobenzoate **1a** with F_3CSO_2Na under different conditions. The deoxygenative and defluorinative processes are essential for the *in situ* formation of F_2CS from F_3CSO_2Na. With the knowledge that a copper catalyst may play a role in deoxygenation and defluorination,[15, 16] the reaction was carried out in the presence of 5 mol% CuI at 110 °C in different solvents, including toluene, MeCN, THF, DCE, DMF and EtOH (entries 1–6). When the reaction was conducted in toluene, product **2** was obtained in 38% yield (entry 1). To further improve the reaction conditions, $HPO(OEt)_2$ was added as a deoxygenating agent to the reaction.[5b] Encouragingly, product **2** was obtained in 85% yield when a combination of CuI (5 mol%) and $HPO(OEt)_2$ (2 equiv) was used (entry 7). The desired product was still obtained when the reaction was

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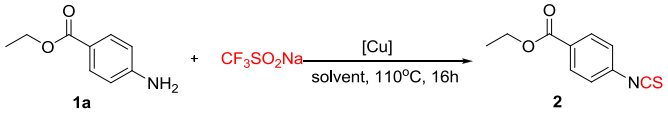
carried out in the absence of CuI, albeit with a lower yield of 56% yield (entry 8). The use of 5 mol% CuI gave a better yield compared to when 10 mol% or 2 mol% CuI was used (entries 9 and 10, respectively). Decreasing the loading of $HPO(OEt)_2$ to one equivalent led to a corresponding reduction in yield (entry 11). The optimal reaction temperature was found to be 110 °C, with neither a decrease nor increase in temperature improving the yield (entries 13-15). Other copper catalysts such as CuCl, CuBr, Cu_2O, CuOAc and $Cu(OAc)_2$ were examined. These copper catalysts either gave poor yields or were completely ineffective (entries 16–20). We speculated that the generation of HF may prohibit the isothiocyanation, and that the capture of HF by base may facilitate the transformation. However, the addition of Et_3N completely depressed the reaction, and the use of K_3PO_4 resulted in a decrease in yield (entries 21 and 22).

Table 1. Screening of Optimal Conditions [a]



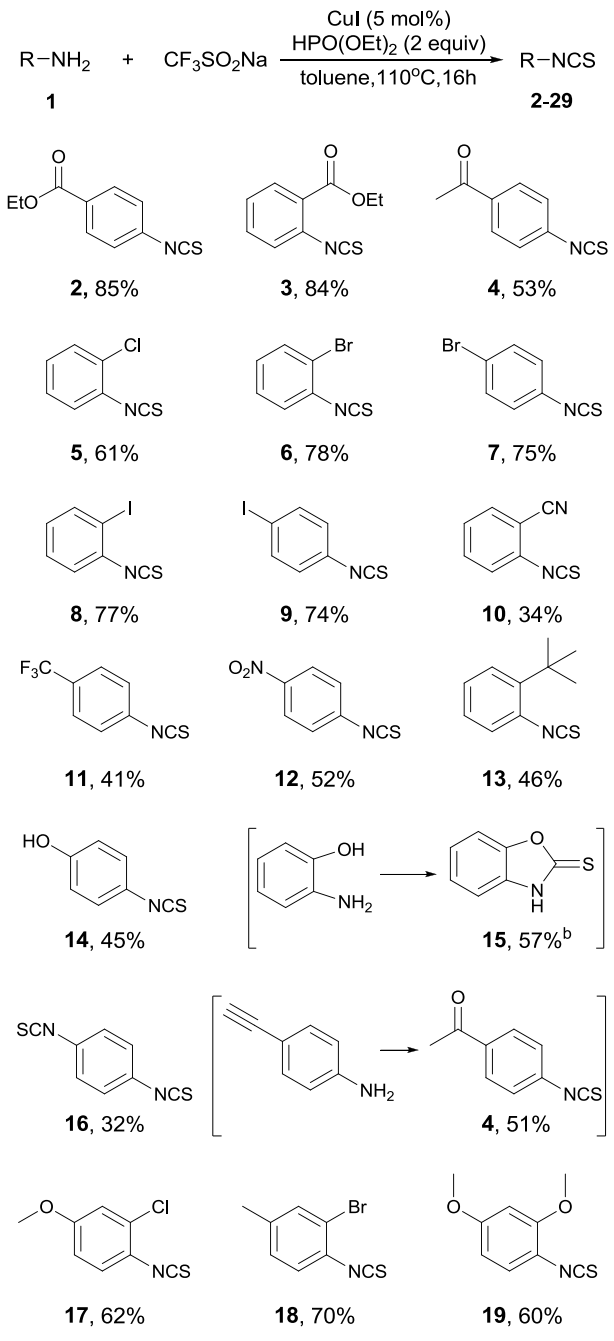
Entry	Catalyst (mol%)	Addition	Temperature (°C)	Solvent	Isolated Yield (%)
1	CuI (5)	—	110	Toluene	38
2	CuI (5)	—	110	MeCN	33
3	CuI (5)	—	110	THF	0
4	CuI (5)	—	110	DCE	Trace
5	CuI (5)	—	110	DMF	0
6	CuI (5)	—	110	EtOH	0
7	CuI (5)	$HPO(OEt)_2$	110	Toluene	85
8	—	$HPO(OEt)_2$	110	Toluene	56
9	CuI (10)	$HPO(OEt)_2$	110	Toluene	74
10	CuI (2)	$HPO(OEt)_2$	110	Toluene	65
11[b]	CuI (5)	$HPO(OEt)_2$	110	Toluene	73
12[c]	CuI (5)	$HPO(OEt)_2$	110	Toluene	84
13	CuI (5)	$HPO(OEt)_2$	90	Toluene	63
14	CuI (5)	$HPO(OEt)_2$	120	Toluene	71
15	CuI (5)	$HPO(OEt)_2$	140	Toluene	75
16	CuCl (5)	$HPO(OEt)_2$	110	Toluene	30
17	CuBr (5)	$HPO(OEt)_2$	110	Toluene	35
18	Cu_2O (5)	$HPO(OEt)_2$	110	Toluene	0
19	CuOAc (5)	$HPO(OEt)_2$	110	Toluene	30
20	$Cu(OAc)_2$ (5)	$HPO(OEt)_2$	110	Toluene	trace
21[d]	CuI (5)	$HPO(OEt)_2$	110	Toluene	trace
22[e]	CuI (5)	$HPO(OEt)_2$	110	Toluene	56

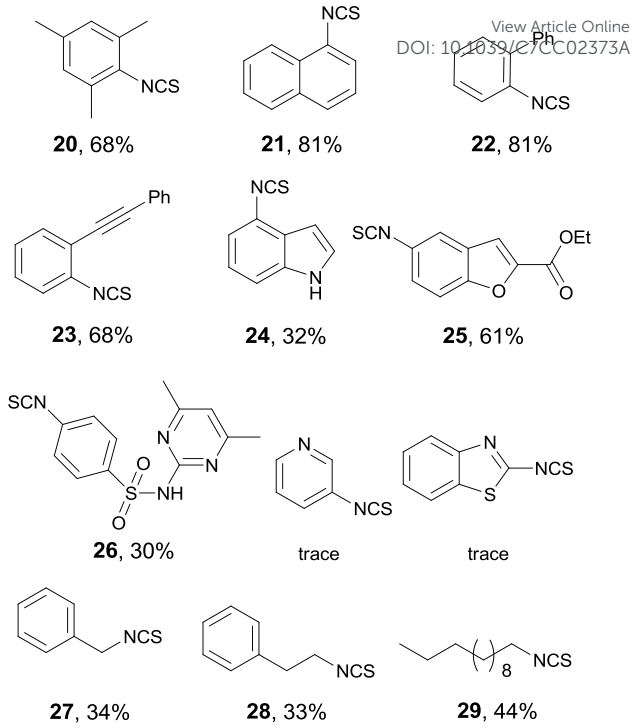
[a] Reaction conditions: **1a** (0.1 mmol), [Cu] (5 mol%), CF_3SO_2Na (0.2 mmol), $HPO(OEt)_2$ (0.2 mmol) was heated at 110°C in solvent (1 mL). [b] $HPO(OEt)_2$ (1 equiv). [c] $HPO(OEt)_2$ (2 equiv). [d] Et_3N (1 equiv) was added. [e] K_3PO_4 (1 equiv) was added.

With the optimized reaction conditions in hand (Table 1, entry 7), the scope of amines was investigated (Table 2). Aromatic amines with diverse functional groups were well tolerated to afford the corresponding products in moderate to good yields (Table 2). These functional groups include ester, acetyl, chlorine, bromine, iodine, cyano, trifluoromethyl, nitro, methoxy, *t*-butyl, hydroxyl, and phenyl groups. All of these functional groups are synthetically useful in medicinal chemistry. Aromatic amines bearing an ester group at the *ortho*- or *para*-positions of the aromatic ring gave their corresponding products in good yields (products **2** and **3**). Halo-substituted aromatic amines underwent isothiocyanation smoothly to afford diverse halo-substituted isothiocyanates which can be readily modified via cross-coupling reactions (products **5–9**). Although strong electron-withdrawing groups such as cyano, trifluoromethyl, and nitro reduce the reactivity of aromatic amines, the reaction still proceeded well with substrates bearing these functionalities (products **10–12**). The substrate with a bulky *t*-butyl group also underwent the reaction to afford product **13** in 46% yield. It is noteworthy that 4-aminophenol bearing a hydroxyl group is also compatible with the reaction conditions, providing its corresponding product **14** in 45% yield; whereas the isothiocyanation of 2-aminophenol undergoes a further intramolecular nucleophilic addition to give benzo[d]oxazole-2(3H)-thione **15** (an important pharmaceutical intermediate) in 57% yield. The double isothiocyanation of benzene-1,4-diamine could be achieved under the standard conditions, albeit with the corresponding product **16** being obtained in only 32% yield. Interestingly, the reaction of 4-ethynylaniline still proceeded smoothly with the transformation of the terminal alkyne to an acetyl group. Di-substituted aromatic amines such as 2-chloro-4-methoxyaniline, 2-bromo-4-methylaniline, and 2,4-dimethoxyaniline were all amenable to the reaction conditions to give their corresponding products in moderate yields (products **17–19**). 2,4,6-Trimethylaniline also performed well to afford product **20** in 68% yield. Naphthalen-1-amine performed particularly well to afford product **21** in 81% yield, suggesting that the aromatic conjugation may contribute to the good yield. Steric effects had no significant impact on the reaction. For example, the *o*-phenyl or *o*-phenylethynyl substituted aromatic amines performed well to give the corresponding products **22** and **23** in 81% and 68% yields, respectively. It is noteworthy that product **23** is a synthetically useful building block for the construction of polycyclic compounds.[17] Importantly, several useful heteroaromatic amines such as indole, furan, and sulfonamide derivatives are also compatible with the reaction conditions, compounds which are of great interest in drug design and discovery (products **24–26**). However, both 3-aminopyridine and 2-aminobenzothiazole are not suitable substrates for the reaction, suggesting that the basicity of *N*-heterocycles might prohibit the reaction. The isothiocyanation of benzylamine and

phenylethylamine was also carried out. Although the respective products, **27** and **28**, are both volatile and moisture sensitive, they were obtained in 34% and 33% yields, respectively. To our delight, dodecan-1-amine could also undergo the isothiocyanation to provide product **29** in 44% yield. Generally, in the isothiocyanation reactions, a small amount of starting materials and a by-product ethyl arylcarbamate were observed on GC-MS. It is demonstrated that the formed isothiocyanates could further react with ethanol (from the decomposition of $HPO(OEt)_2$) to afford the corresponding ethyl arylcarbamates.

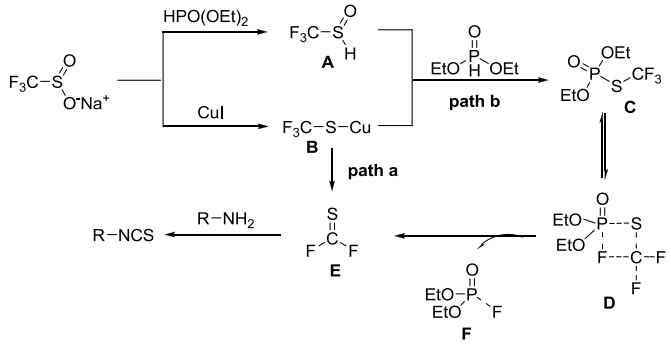
Table 2. The scope of amines [a]





[a] Reaction conditions: **1a** (0.2 mmol), CuI (5 mol%), CF_3SO_2Na (0.4 mmol), $HPO(OEt)_2$ (0.4 mmol), in toluene (2 mL) at 110 °C for 16h. [b] in a mixture solvent of toluene (1.8 mL) and DMF (0.2 mL).

Based on the present results and previous reports concerning the chemistry of CF_3SO_2Na,[5,6] two possible reaction pathways shown in Scheme 2 are proposed. Due to the fact that the reaction proceeds with CuI or $HPO(OEt)_2$ alone (table 1, entries 1 and 8), we speculate that CF_3SO_2Na may react with the CuI to produce F_3CSCu (**B**), while reaction with $HPO(OEt)_2$ affords intermediate **A**.[5b,6a] Both intermediates, **A** and **B**, can further react with $HPO(OEt)_2$ to yield intermediate **C**. In 1989, Łopusiński reported that a slow extrusion of thiocarbonyl fluoride **E** was observed when Intermediate **C** was treated at 100°C in aprotic solvent.[6c] Thus thiocarbonyl fluoride **E** may be formed from Intermediate **C** via a defluorination process involving transition state **D**. In this reaction step, the phosphonate might be transformed to diethyl phosphorofluoridate **F**, which was observed by GC-MS analysis (see the supporting information). Under heating, F_3CSCu (**B**) may undergo direct defluorination leading to the *in situ* formation of thiocarbonyl fluoride **E**.[6a] Finally, the thiocarbonyl fluoride reacts with the primary amine to form the corresponding isothiocyanate product. A more detailed reaction mechanism remains to be investigated.



Scheme 2 Possible mechanisms

Conclusions

In summary, the first synthesis of aromatic isothiocyanates employing the Langlois reagent as an effective isothiocyanating agent has been reported. A variety of synthetically useful functional groups and heterocycles are tolerated under the reaction conditions, which will be of great interest to medicinal chemists. The use of Langlois reagent in place of highly toxic phosgene or thiophosgene provides an operationally simple, safe, and environmentally benign synthetic route to aromatic isothiocyanates.

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