Four-Component Synthesis of Imidazolinium-Fused Heterocycles from Ugi–Smiles Couplings

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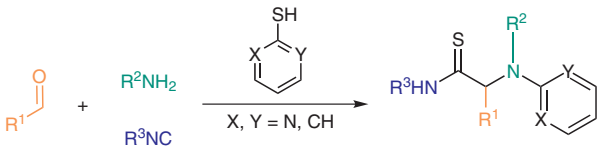
Received 8 October 2009

Abstract: New imidazolinium-fused scaffolds are synthesized via a one-pot, two-step procedure involving a Ugi–Smiles coupling of mercaptotriazine derivatives with an isocyanide, an aldehyde, and a primary amine.

Key words: triazine, mercaptan, Ugi–Smiles, multicomponent reaction, thioamide

Compared to their related amides, thioamides show an increased reactivity due to the heightened nucleophilicity of the sulfur atom, enhanced by a rather weak carbon–sulfur double bond. Their extensive use as synthetic intermediates for the preparation of various heterocycles,[1] as well as their interesting biological activities as peptidomimetics,[2] have spurred chemists on to seek new methods for their preparation.[3] Following our interest on multicomponent reactions involving isocyanides,[4] we have recently disclosed a four-component access to complex thioamides based on the Ugi–Smiles coupling of heteroaromatic mercaptans (Scheme 1).[5]



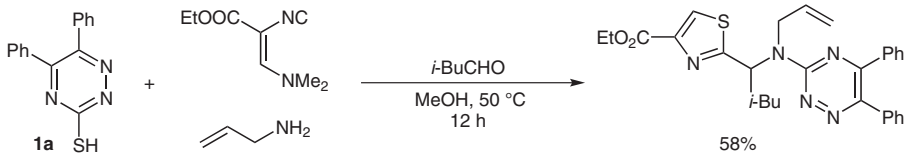
Scheme 1 Ugi–Smiles multicomponent thioamide synthesis

The couplings with mercaptans give rather contrasting results. Indeed, whereas *ortho*- and *para*-nitrothiophenols fail to give any coupling with an isocyanide, an aldehyde, and an amine, heteroaromatic mercaptans such as 2-mercaptobenzooxazoles or benzothiazoles give the expected adducts in fair to good yields (it is interesting to note that the corresponding hydroxy derivatives are not reactive under similar conditions).[6] Following our study on pyridine and pyrimidine derivatives, we now wish to report our results on the behavior of triazines, as well as the transformation of the resulting thioamides into new imidazolinium-fused heterocycles in a one-pot process.

Thiopyridines and thiopyrimidines being prone to interact in a Ugi–Smiles reaction, we assumed that the introduction of an additional nitrogen atom in the cycle would favor the process by lowering the electron density on the aromatic carbon atom. To our delight, 3-mercapto-1,2,4-triazines turned out to be among the most efficient acidic partners in Ugi–Smiles couplings. The four-component reaction (4-CR) proceeded smoothly at 50 °C in methanol using stoichiometric amounts of each component. The reaction seems to be quite general, as various aldehydes; aliphatic aldehydes, even hindered ones (Table 1, entries 1–9), as well as aromatic aldehydes (Table 1, entry 10) gave good results. Most noteworthy, the Ugi–Smiles couplings of ketones whose reaction times traditionally range from 1–10 days are much faster with the triazine **1a** as a surrogate acidic input for the Ugi reaction and give the corresponding adducts in good yields (Table 1, entry 11–13).

The efficiency of the triazine **1a** in triggering the process is further demonstrated by the use of the Schöllkopf isocyanide, which forms thiazoles through an Ugi–Smiles–cyclocondensation cascade (Scheme 2).[7]

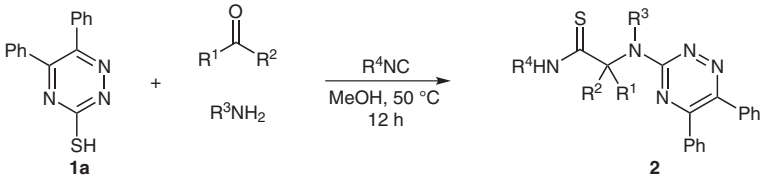
In order to assess the scope of this coupling, two additional mercaptotriazines were prepared by condensing a thiosemicarbazide and a dicarbonyl compound.[8] With the monosubstituted triazine compound **1b**, the 4-CR occurs with similar yields to those obtained with the triazine **1a**, even in the case of ketones (Table 2, entries 1–4). However, the bis(2-pyridinyl)mercaptotriazine (**1c**) is less efficient in this coupling, as the yields do not exceed 50%

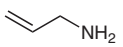
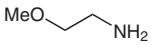
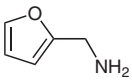
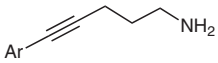
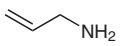
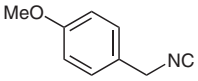
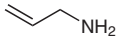
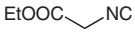
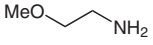
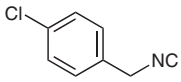
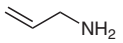
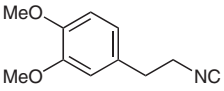
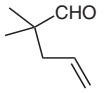
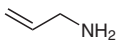
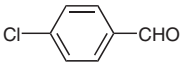
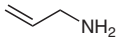
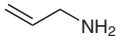
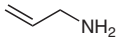
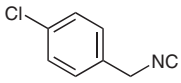
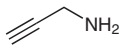
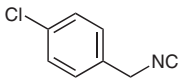


Scheme 2 Ugi–Smiles–cyclocondensation cascade

SYNLETT 2010, No. 1, pp 0153–0157
Advanced online publication: 14.12.2009
DOI: 10.1055/s-0029-1218550; Art ID: D28409ST

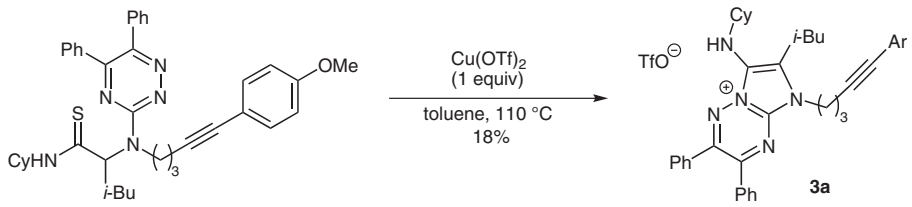
Table 1 Ugi–Smiles Couplings with Triazine **1a**



Entry	R^1COR^2	R^3NH_2	R^4NC	Product	Yield (%)
1	*i*-BuCHO		CyNC	**2a**	93
2	*i*-BuCHO		CyNC	**2b**	98
3	*i*-BuCHO		CyNC	**2c**	79
4	*i*-BuCHO		CyNC	**2d**	21
5	*i*-BuCHO			**2e**	86
6	*i*-BuCHO			**2f**	84
7	*i*-BuCHO			**2g**	93
8	*i*-BuCHO			**2h**	95
9			CyNC	**2i**	42
10			CyNC	**2j**	47
11			CyNC	**2k**	95
12				**2l**	76
13				**2m**	78

(Table 2, entries 5 and 6). This method constitutes an easy path to functionalized thioamides that would otherwise be difficult to obtain.

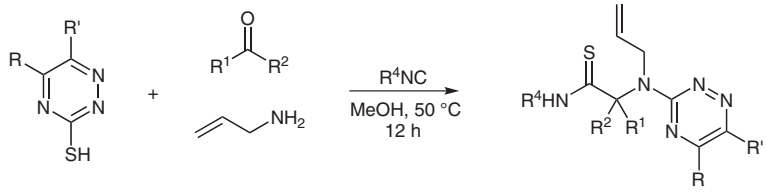
The high-yielding couplings observed with some of these triazines prompted us to examine the chemistry of these adducts in order to establish further one-pot syntheses of complex heterocycles. Triazines are known to undergo intramolecular [4+2] cycloadditions with the elimination of nitrogen,[9] these reactions having been recently exploited with Ugi adducts by the Zanze group.[10] The initial trials with the thioamide **2d** in toluene at reflux, or even at higher temperatures under microwave irradiation, failed to give any cyclized product. During several attempted acti-

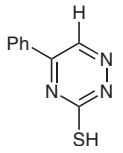
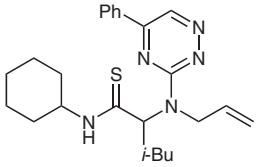
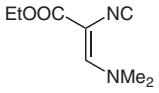
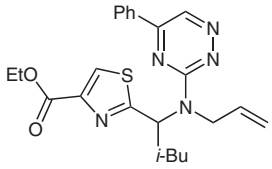
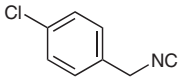
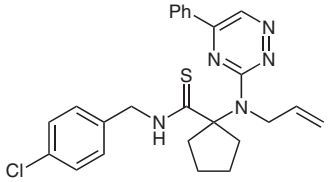
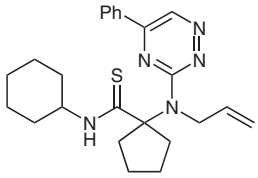
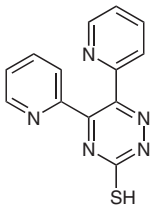
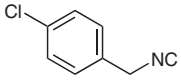
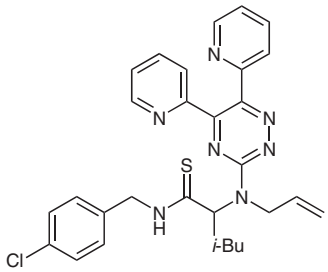
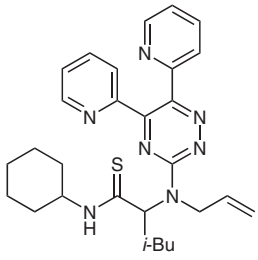


Scheme 3 Triazolino imidazolinium formation

vations of the heterocycle with copper salts, traces of a highly colored product involving a cyclization with the thioamide function were observed. When one equivalent of copper(II) trifluoromethanesulfonate was used in toluene at 110 °C, the triazolino imidazolinium salt **3a** was obtained in a 18% isolated yield (Scheme 3).

Table 2 Couplings with Different Triazines



Entry	ArSH	R^1COR^2	R^4NC	Product and yield (%)
1	 **1b**	*i*-BuCHO	CyNC	 **2n** 74
2	**1b**	*i*-BuCHO		 **2o** 45
3	**1b**			 **2p** 53
4	**1b**		CyNC	 **2q** 72
5	 **1c**	*i*-BuCHO		 **2r** 43
6	**1c**	*i*-BuCHO	CyNC	 **2s** 45

As this cyclization involves two new functionalities introduced in the Ugi–Smiles step, we decided to focus on this reaction and to optimize the formation of this fused system in a one-pot sequence starting directly from the four components involved in the Ugi coupling. With the triazine **1b**, isovaleraldehyde, allylamine, and cyclohexylisocyanide (Table 2, entry 1), we devised conditions in which the Ugi–Smiles step is performed in refluxing toluene (1 M) for two hours followed by dilution of the medium with toluene to a concentration of 0.1 M and addition of the copper salt. The final imidazolinium salt **3b** was obtained in 69% isolated yield after refluxing the mixture for three hours (Table 3, entry 1). The presence of the triflate counterion was confirmed by an X-ray crystal structure analysis performed on this imidazolinium salt (Figure 1).[11]

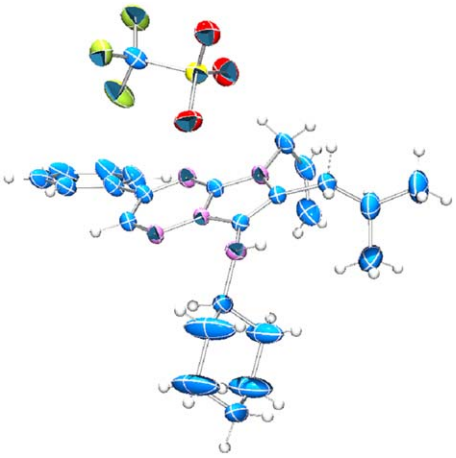
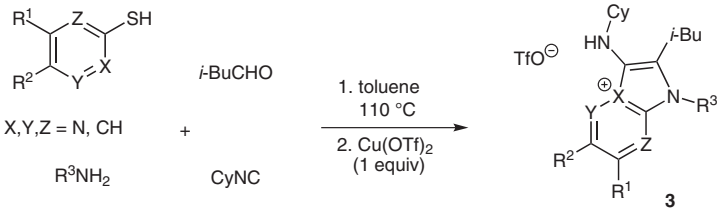
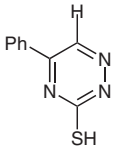
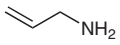
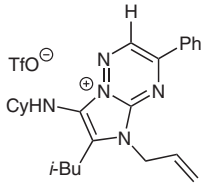
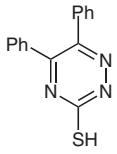
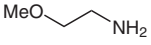
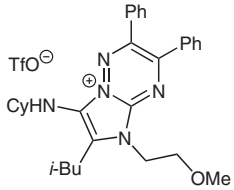
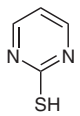
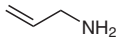
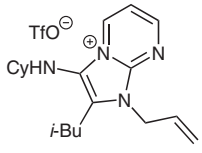
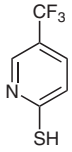
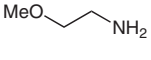
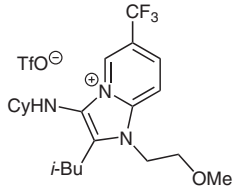


Figure 1 X-ray crystal structure of compound **3b**

The diphenyl-substituted triazine **1a** behaved similarly, giving the fused imidazolinium triflate **3c** (Table 3, entry

Table 3 Formation of Different Imidazolinium Salts



Entry	ArSH	R^2NH_2	Time (step 1)	Time (step 2)	Product and yield
1	 **1b**		2 h	1 h	 **3b** 69%
2	 **1a**		2 h	36 h	 **3c** 63%
3[a]			4 d	2 h	 **3d** 85%
4			2 h	12 h	 **3e** 95%

[a] The first step was performed neat at 90 °C, followed by the copper addition in toluene (to a concentration of 0.1 M).

2). Such a process can be extended to other nitrogenated heterocycles. For instance, when submitted to a neat four-component coupling – with allylamine, isovaleraldehyde, and cyclohexylisocyanide – followed by a copper-induced cyclization, 2-mercaptopyrimidine gave the corresponding pyrimidinyl imidazolinium salt in a 85% yield (Table 3, entry 3), whilst the pyridinyl analogue was obtained in excellent yields as well (Table 3, entry 4).

In conclusion, we have disclosed a new family of highly efficient acidic inputs in Ugi–Smiles reactions. Mercaptotriazines, the diphenyl-substituted **1a** in particular, allow the formation of Ugi–Smiles thioamides with short reaction times and with better yields than the related reactions with mercapto- or hydroxypyridines and pyrimidines. The synthetic value of these thioamides[12] has been further demonstrated in a one-pot preparation of fused imidazolinium salts.

Typical Procedure for the Synthesis of Thioamide 2a (Table 1, Entry 1)

To a solution of 265 mg (1.0 mmol, 1.0 equiv) of 5,6-diphenyl-1,2,4-triazine-3-thiol in MeOH (1 mL) were added allylamine (75 μL, 1.0 mmol, 1.0 equiv), isovaleraldehyde (108 μL, 1.0 mmol, 1.0 equiv), cyclohexylisocyanide (110 μL, 1.0 mmol, 1.0 equiv). The resulting mixture was stirred at 55 °C for 12 h. The solvent was then removed in vacuo. The crude product was purified by flash chromatography on silica gel (Et_2O–PE = 10:90) to give 464 mg (93%) of **2a**. Mp 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.12 (br s, 1 H), 7.56–7.48 (m, 4 H), 7.47–7.41 (m, 1 H), 7.39–7.32 (m, 5 H), 6.08–5.96 (m, 1 H), 5.53 (br s, 1 H), 5.33 (d, *J* = 17.4 Hz, 1 H), 5.21 (dd, *J* = 10.1, 1.0 Hz, 1 H), 4.59 (dd, *J* = 16.0, 6.3 Hz, 1 H), 4.47–4.40 (m, 1 H), 4.39–4.30 (m, 1 H), 2.23–2.30 (m, 1 H), 2.07–1.93 (m, 2 H), 1.92–1.81 (m, 1 H), 1.69–1.47 (m, 5 H), 1.41–1.26 (m, 2 H), 1.18–1.07 (m, 2 H), 0.97 (d, *J* = 6.7 Hz, 6 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 200.7, 149.6, 136.5, 136.3, 134.4, 131.0, 133.1, 129.4, 129.0, 128.9, 128.8, 117.7, 66.7, 53.9, 48.3, 40.1, 31.5, 31.2, 25.8, 25.3, 23.2, 23.0. IR (thin film): 3705, 3602, 3029, 2854, 2341, 1581, 1564, 1426 cm^{-1}. HRMS: *m/z* calcd for $C_{30}H_{37}N_5S$: 499.2770; found: 499.2769.

Typical Procedure for the Synthesis of Imidazolinium 3b (Table 3, entry 1)

To a solution of 189 mg (1.0 mmol, 1.0 equiv) of 5-phenyl-1,2,4-triazine-3-thiol in toluene (1 mL) were added allylamine (75 μL, 1.0 mmol, 1.0 equiv), isovaleraldehyde (108 μL, 1.0 mmol, 1.0 equiv), and cyclohexylisocyanide (110 μL, 1.0 mmol, 1.0 equiv). The resulting mixture was stirred at 110 °C for 2 h and was then diluted to a 0.1 M concentration. Copper triflate (362 mg, 1.0 mmol, 1.0 equiv) was added, and the resulting mixture was stirred at 110 °C for 1 h. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (Et_2O) to give 374 mg (69%) of **3b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.31 (s, 1 H), 8.24 (d, *J* = 8.1 Hz, 2 H), 7.68–7.59 (m, 3 H), 6.13–6.04 (m, 1 H), 5.40 (d, *J* = 10.4 Hz, 1 H), 5.29 (d, *J* = 17.2 Hz, 1 H), 5.20 (d, *J* = 5.8 Hz, 2 H), 4.02 (d, *J* = 7.6 Hz, 1 H), 3.45 (br s, 1 H), 2.84 (d, *J* = 7.3 Hz, 2 H), 2.21–2.14 (m, 1 H), 2.01 (br s, 2 H), 1.79 (br s, 2 H), 1.65 (d, *J* = 11.6 Hz, 1 H), 1.37–1.30 (m, 5 H), 1.06 (d, *J* = 6.6 Hz, 6 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 153.2, 140.6, 134.9, 134.0, 132.7, 130.9, 130.7, 130.2, 128.9, 127.2, 120.2, 55.8, 46.9, 34.6, 32.8, 29.0, 25.7, 25.2, 22.9. IR (thin film): 3309, 2930, 2857, 1631, 1602, 1565, 1252, 1158 cm^{-1}. MS: *m/z* calcd for $C_{24}H_{32}N_5$: 390; found: 390.

Acknowledgment

A.B. thanks the MENR for a fellowship. Financial support was provided by the ENSTA and the ANR (CP2D, Muse project).

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