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# Poorly reactive 5-piperazin-1-yl-1,3,4-thiadiazol-2-amines rendered as valid substrates for Groebke–Blackburn type multi-component reaction with aldehydes and isocyanides using TMSCl as a promoter

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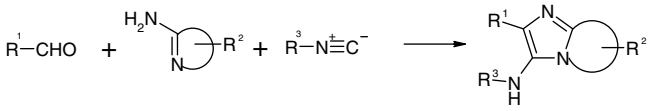
ABSTRACT

N-Substituted 5-piperazin-1-yl-1,3,4-thiadiazol-2-amines that fail to undergo Groebke–Blackburn type MCR with aldehydes and isocyanides provide fair to good yields of the respective 2-piperazin-1-ylimidazo[2,1-*b*][1,3,4]thiadiazoles when such reaction is promoted by an equimolar quantity of trimethylsilyl chloride in aprotic medium. These findings further extend the utility of TMSCl as the isocyanide-based MCR promoter, and also demonstrate that this silicon Lewis acid is the actual promoter of the reaction.


A novel reactivity pattern of 2-aminoazines in multi-component reactions (MCRs) with aldehydes and isocyanides leading to drug-like fused imidazo[1,2-*a*]azines was first reported simultaneously by the Groebke[1] and Blackburn[2] groups in 1998. Shortly afterwards, the same strategy was broadened by Rhone-Poulenc researchers[3] to include 2-aminoazoles as substrates. These pioneering works have led to numerous publications on new types of MCR.[4] In these transformations, the aminoheterocycle component plays a dual role by providing both the amino group and the intercepting nucleophile (the ring nitrogen atom) for the incoming isocyanide. Thus, the two components of the traditional isocyanide-based Ugi MCR—the amine and the carboxylate components—are replaced in the Groebke–Blackburn variant with a single bifunctional reagent, leading to a ring-forming process (Scheme 1).

Among various 2-aminoazoles studied in these reactions to date, only one example[3] of a 1,3,4-thiadiazol-2-amine was shown to provide the respective imidazo[2,1-*b*][1,3,4]thiadiazole in a MCR with benzaldehyde and *tert*-butyl isocyanide (Scheme 2). In our research aimed at utilizing known isocyanide-based MCRs for creating larger compound libraries in a combinatorial fashion,[5,6]



**Scheme 1.** Reaction of 2-aminoazines and -azoles with aldehydes and isonitriles (Groebke–Blackburn reaction).

as well as for developing novel MCRs,[7,8] we envisioned that readily available N-substituted 5-piperazin-1-yl-1,3,4-thiadiazol-2-amines **1** could serve as substrates for Groebke–Blackburn type MCRs. These compounds have already been used[9,10] as starting materials for combinatorial development of various heterocyclic compound libraries (Fig. 1). Their preparation, as described in the literature[9] and modified by us, is outlined in Scheme 3.

Our initial attempts to run the Groebke–Blackburn reaction with a representative starting material **1** (R = Bn), *tert*-butyl isocyanide and *m*-fluorobenzaldehyde proved to be somewhat discouraging. Simple mixing of the three components in methanol and adding a methanolic solution of a mineral acid (catalytic to equimolar quantity of either HCl, $HClO_4$ or $H_2SO_4$) resulted in complex reaction mixtures with a target material content of less than 10%, as estimated by LCMS analyses. This was in contrast with the

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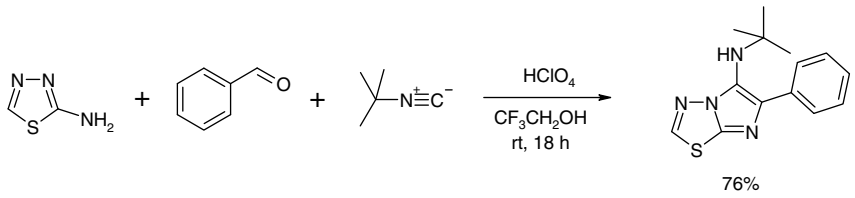



**Scheme 2.** An example[3] of 1,3,4-thiadiazol-2-amine as a partner in a Groebke–Blackburn type reaction.

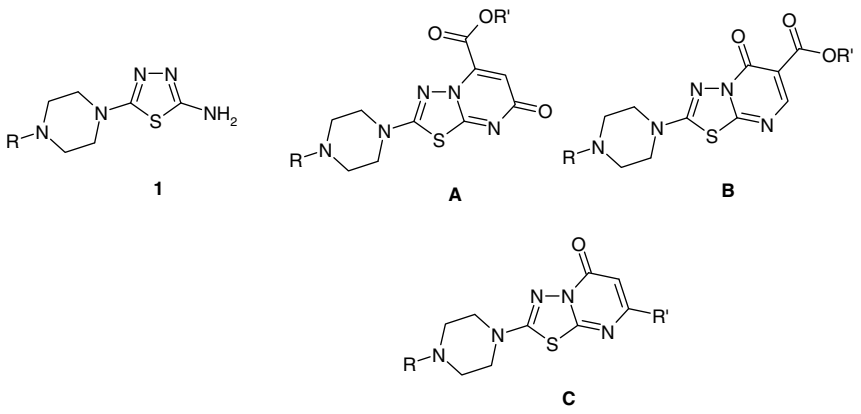
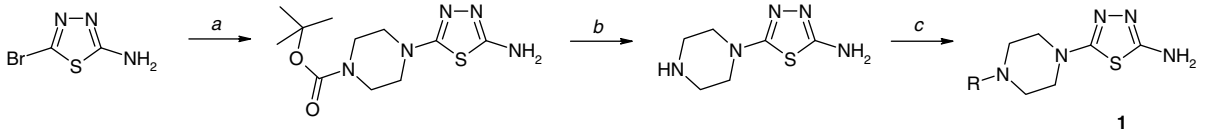



**Figure 1.** N-Substituted 5-piperazin-1-yl-1,3,4-thiadiazol-2-amines (**1**) and examples (**A**,[8] **B**–**C**[9]) of compound libraries incorporating them as part of the core structure.




**Scheme 3.** Preparation of various N-substituted 5-piperazin-1-yl-1,3,4-thiadiazol-2-amines (**1**). Reagents and conditions: (a) *N*-Boc-piperazine (1.1 equiv), $Et_3N$ (1.2 equiv), EtOH reflux, 3 h, 80%; (b) HCl/dioxane, rt, 1 h, quant. yield; (c) R = alkyl: RCHO/$NaBH(OAc)_3$ or RHal/DMF, R = acyl: R′COCl/pyridine, R = carbamoyl: R′NCO/DCM.

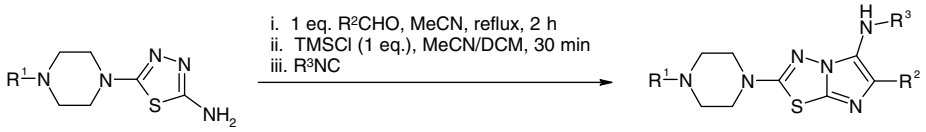
unsubstituted 1,3,4-thiadiazol-2-amine example reported.[3] We therefore decided to attempt the desired Groebke–Blackburn reaction using a Lewis acid as promoter instead. After screening a small set of Lewis acids, we found that a catalytic (0.2 equiv.) or even equimolar amount of metal triflates such as $Yb(OTf)_3$ or $Sc(OTf)_3$ (as initially used by Blackburn[2]) led to better yields of the target material (25–30%, as judged by LCMS analyses of the reaction mixtures). However, isolation of the target was complicated by the presence of several unidentified by-products. A similar degree of conversion (~25%) was achieved when trimethylsilyl chloride (TMSCl) was used as the promoter under the same reaction conditions (1 equiv TMSCl, MeOH, rt, 18 h) as those recently employed by us to promote the MCR of ethylenediamine with carbonyl compounds and isocyanides.[7] Despite the low conversion, the TMSCl-promoted reaction offered a clear advantage over other methods tested as it gave virtually no by-products. After some additional experimentation that involved changing the reaction medium (EtOH, AcOH, MeCN) as well as the order of mixing the reactants, we arrived at an optimized reaction protocol that allowed preparation and easy purification of various 2-piperazin-1-ylimidazo-[2,1-*b*][1,3,4]thiadiazoles **2** as summarized in Table 1.

The optimized protocol involved mixing equimolar amounts of the starting amine **1** and an aldehyde in anhydrous MeCN and heating the resulting solution at reflux for 2 h to ensure complete formation of the respective imine intermediate.[11] The reaction mixture was then cooled to room temperature and evaporated to dryness. The solid residue was further dried by addition of toluene and concentration of the resulting suspension in vacuo (repeated twice). The residue was then suspended in anhydrous MeCN and treated with a solution of an equimolar amount of TMSCl in anhydrous DCM. The mixture was stirred at ambient temperature for 30 min (in most cases the suspension cleared), and then treated with a solution of isocyanide (1 equiv) in MeCN and heated at 70 °C overnight. At this stage, all of the reactions described herein were complete by LCMS analyses (as judged by the disappearance of **1**). In a number of cases the products isolated by filtration were at least 90% pure as judged from LCMS and $^1H$ NMR data. In some cases, chromatographic isolation of the products was required (silica gel, eluted by appropriate gradients of 0→10% methanol in dichloromethane). All of the synthesized compounds were characterized by $^1H$ and $^{13}C$ NMR, LCMS and elemental analyses.[12]

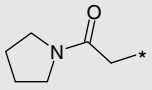
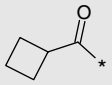
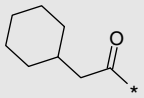
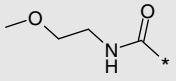
The use of aprotic solvents as the reaction medium is worthy of note. In our previous work,[7] TMSCl was used as a promoter for isocyanide-based MCRs in methanol, and thus there was some room for arguing that a low concentration of HCl resulting from reaction of TMSCl with methanol could be the actual catalyst for the reaction. This possibility was partly ruled out by using a HCl solution in dioxane, which provided inferior results compared to those of TMSCl. The present work, in our opinion, could be considered as further proof of the silicon-based Lewis acid being the effective reaction promoter, as presumably no HCl is generated in aprotic anhydrous solvents.

In conclusion, we have developed a robust synthetic protocol for the Groebke–Blackburn MCR using TMSCl as a promoter. This protocol allows the use of N-substituted 5-piperazin-1-yl-1,3,4-thiadiazol-2-amines as substrates for this reaction, a process that

**Table 1**
TMSCl-promoted MCRs of N-substituted 5-piperazin-1-yl-1,3,4-thiadiazol-2-amines **1**, aldehydes and isonitriles




**1** **2**

| Entry | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|
| **a** | 2-$PyCH_2$ | 4-$EtC_6H_4$ | Cyclopentyl | 78[a] |
| **b** | Allyl | 4-$MeC_6H_4$ | cyclopentyl | 72[a] |
| **c** | 3-$MeOC_6H_4CH_2$ | 4-$FC_6H_4$ | *tert*-Butyl | 84[a] |
| **d** | Bn | 3-$FC_6H_4$ | *tert*-Butyl | 92[a] |
| **e** |  | Ph | *tert*-Butyl | 56[a] |
| **f** | 3-$ClC_6H_4CH_2$ | Ph | *tert*-Butyl | 75[a] |
| **g** | 4-$NCC_6H_4CH_2$ | Ph | *tert*-Butyl | 88[a] |
| **h** |  | 4-$EtC_6H_4$ | *tert*-Butyl | 67[b] |
| **i** |  | 3-$MeC_6H_4$ | *tert*-Butyl | 48[b] |
| **j** | 4-$FC_6H_4CO$ | 3-$MeC_6H_4$ | *tert*-Butyl | 78[b] |
| **k** | *tert*-BuNHCO | 4-$EtC_6H_4$ | Cyclopentyl | 92[b] |
| **l** |  | 4-$FC_6H_4$ | Cyclopentyl | 69[b] |

[a] Yield after chromatography.
[b] Yield after product isolation by simple filtration (total yield may be higher).

we found to be inefficient under the standard reaction conditions reported in the literature. These findings further extend the applicability of trimethylchlorosilane as an efficient equimolar promoter of isocyanide-based MCRs and reagent, which often appears to be the only workable metal-free Lewis acid alternative to traditional Brønsted acid catalysts. We are currently in the process of extending these findings to other 2-aminoazole substrates. The results of these studies will be reported in due course.

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10. Compound libraries **B**–**C** are part of the ChemDiv (www.chemdiv.com) screening compound collection.
11. We have observed that the complete formation of the imine intermediate prior to the addition of other reactants and the promoter is essential: it suppresses by-product formation and also ensures an unambiguous regiochemical course of the Groebke–Blackburn MCRs. Simple mixing of all the reaction components and an acid catalyst in a polar solvent can lead (as was observed for various 2-aminoazines by us[5] and others[4e]) to concomitant formation of the undesired regioisomer. For a thorough insight into possible regiochemical outcomes of the Groebke–Blackburn reaction, see: Mandair, G. S.; Light, M.; Russell, A.; Hursthouse, M.; Bradley, M. *Tetrahedron Lett.* **2002**, *43*, 4267–4269.
12. *Representative characterization data for the synthesized compounds*: Compound **2d**—grey solid, mp = 186 °C (decomp.); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.85–7.97 (m, 2H), 7.23–7.39 (m, 6H), 6.90–6.70 (m, 1H), 4.20 (br s, 1H), 3.56 (s, 2H), 3.40–3.49 (m, 4H), 2.52–2.57 (m, 4H), 1.10 (s, 9H); $^{13}$C NMR (75 Hz, DMSO-$d_6$) $\delta$ 161.9 (d, $J_{C-F}$ = 260.3 Hz), 161.2, 158.9, 138.5, 133.9 (two lines), 129.5 (d, $J_{C-F}$ = 6.8 Hz), 128.8, 128.3, 127.4, 121.5 (two lines), 112.0 (d, $J_{C-F}$ = 29.0 Hz), 110.5 (d, $J_{C-F}$ = 28.5 Hz), 95.4, 61.8, 54.9, 51.4, 48.1, 30.1; LCMS (M+H) 465; Anal. Calcd for $C_{25}H_{29}FN_6S$: C, 64.63; H, 6.29; N, 18.09. Found: C, 64.70; H, 6.33; N, 18.17. Compound **2j**—off-white solid, mp = 172–176 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.95 (s, 1H), 7.90 (d, $J$ = 7.9 Hz, 1H), 7.49–7.57 (m, 2H), 7.26–7.34 (m, 2H), 7.16–7.22 (m, 1H), 6.96 (d, $J$ = 7.4 Hz, 1H), 4.17 (br s, 1H), 3.43–3.71 (br m, 8H), 2.30 (s, 3H), 1.08 (s, 9H); $^{13}$C NMR (75 Hz, DMSO-$d_6$) $\delta$ 168.5, 163.1, 162.6 (d, $J_{C-F}$ = 245.1 Hz), 136.6, 136.2, 134.7, 131.9, 129.7 (d, $J_{C-F}$ = 8.6 Hz), 127.7, 126.7, 126.4, 122.9, 115.5 (d, $J_{C-F}$ = 21.7 Hz), 95.5, 54.8, 47.9, 30.2, 21.2; LCMS (M+H) 493; Anal. Calcd for $C_{26}H_{29}FN_6OS$: C, 63.39; H, 5.93; N, 17.06. Found: C, 63.43; H, 6.00; N, 17.12. Compound **2l**—grey solid, mp = 154–156 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.01–8.08 (m, 2H), 7.11–7.19 (m, 2H), 6.71 (br t, $J$ = 5.1 Hz, 1H), 4.42 (br d, $J$ = 4.3 Hz, 1H), 3.77–3.85 (m, 1H), 3.32–3.50 (m, 10H), 3.24 (s, 3H), 3.15–3.23 (m, 2H), 1.42–1.73 (m, 8H); $^{13}$C NMR (75 Hz, DMSO-$d_6$) $\delta$ 163.8, 160.4 (d, $J_{C-F}$ = 241.1 Hz), 157.2, 135.8, 131.8, 131.1, 128.5, 126.6 (d, $J_{C-F}$ = 7.4 Hz), 114.8 (d, $J_{C-F}$ = 21.1 Hz), 95.5, 71.3, 66.4, 57.9, 47.8, 42.5, 32.5, 23.4; LCMS (M+H) 488; Anal. Calcd for $C_{23}H_{30}FN_7O_2S$: C, 56.66; H, 6.20; N, 20.11. Found: C, 56.71; H, 6.25; N, 20.16.