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TMSCl-promoted isocyanide-based MCR of ethylenediamines: an efficient assembling of 2-aminopyrazine core

Volodymyr Kysil,[a,*] Sergey Tkachenko,[a] Alexander Khvat,[a] Caroline Williams,[a] Sergey Tsirulnikov,[b] Marina Churakova[b] and Alexandre Ivachtchenko[a]

[a]*ChemDiv, Inc., 6605 Nancy Ridge Dr., San Diego, CA 92121, USA*
[b]*Chemical Diversity Research Institute, 114401 Khimki, Moscow Reg., Russia*

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Abstract—New trimethylchlorosilane (TMSCl) promoted multicomponent reaction (MCR) of ethylenediamine(s), diverse carbonyl compounds, and isocyanides is proposed for the synthesis of a variety of highly substituted 3,4,5,6-tetrahydropyrazin-2-amines including corresponding spirocyclic compounds.

Structural fragments of 3,4,5,6-tetrahydropyrazin-2-amine **1A** (Fig. 1) as well as tautomeric piperazin-2-imine **1B** are key core elements of various natural[1,2] and biologically active molecules (for the most recent examples, see[3–6]) including anticancer multidrug resistance reversal agents.[7] The development of new and convenient synthetic approaches to these scaffolds is therefore of great interest to the medicinal chemistry community.

Due to the convenience and high degree of atom economy, multicomponent reactions (MCR) have become one of the most efficient tools for rapid scaffold construction and introduction of molecular diversity.[8,9] Isocyanide-based MCRs (IMCR), as an efficient approach to a multitude of peptide-like heterocyclic scaffolds, have arguably become the most successful among them.[10–13] According to recently published reviews,[10,13–15] IMCR strategies have been employed successfully for the synthesis of four types of piperazine cores, namely 2,6- and 2,4-diketopiperazines, 3-ketopiperazine-2-carboxamides, and piperazine-2-carboxamides. IMCR strategies also proved to be effective for the synthesis of highly substituted tetra- and dihydropyrazin-2-ones.[16–18] At the same time, there is only limited data on synthesis of the tetrahydropyrazin-2-amines and piperazin-2-imines. Thus, IMCR has been employed for the synthesis of tetrazolopyrimidines[19,20] and pyrido[1,2-*a*]pyrazines[21,22] with a formal imino(amino)piperazine core.

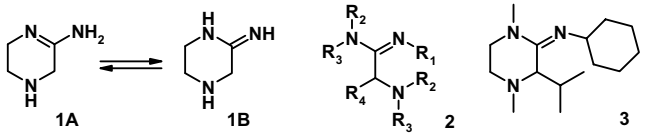

Figure 1.

Within this context, our attention was attracted by the approach, recently published by Keung et al.,[23] to highly substituted aminoacetamidines **2** based on Lewis acid (LA) mediated MCR of isocyanide, aldehyde, and 2 equiv of amine. Scandium(III) triflate demonstrated the highest activity among LAs examined. Only one example of the 1,4-dimethyl piperazin-2-imine **3** synthesis is described in this work when *N*,*N*′-dimethylethylenediamine was used instead of 2 equiv of the amine in condensation with 2-methylpropanal and cyclohexylisocyanide. We were intrigued by this reaction because of its potential use for diverse functionalized piperazines syntheses.

Development of an IMCR-based approach to new diverse substituted 2-amino-3,4,5,6-tetrahydropyrazines capable of further transformations was the goal of our present work. In particular, we were interested in reactions of *N*,*N*′-unsubstituted ethylenediamine(s) with

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* Corresponding author. Tel.: +1 858 794 4860; fax: +1 858 794 4931; e-mail addresses: vkysil@chemdiv.com; av@chemdiv.com

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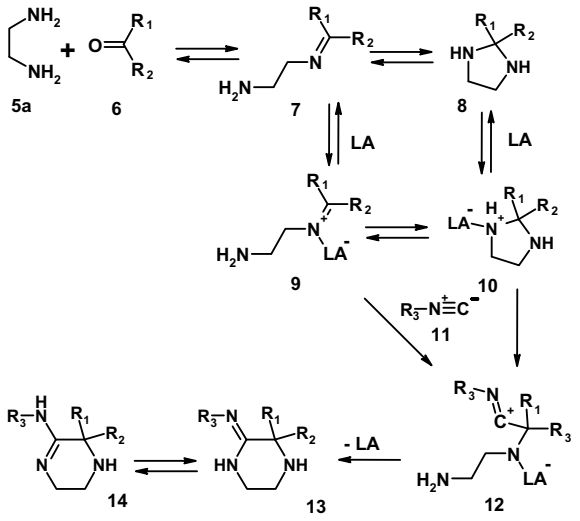


Scheme 1.

carbonyl compounds and isocyanides. A possible reaction scenario is shown in Scheme 1.

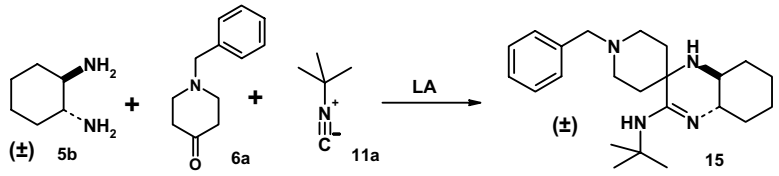
Azomethynes **7** formed from ethylenediamine **5a** and carbonyl compounds **6** are able to exist in equilibrium with their corresponding cyclic aminals (imidazolidines) **8**.[24–26] Each of these ring-chain tautomeric forms is able to react with nucleophiles, in our case—with isocyanides **11**, and activation of both is required for the reaction to proceed. The activated intermediates **9** and **10** should convert to the same intermediate **12**, which upon cyclization might yield pyperazin-2-imine **13** or tautomeric tetrahydropyperazin-2-amine **14**.

Initially, we investigated the reaction of *tert*-butylisocyanide **11a** with *N*-benzyl-4-piperidone **6a** and *trans*-cyclohexane-1,2-diamine **5b**. Both chosen starting materials, carbonyl **6a** and diamine **5b** components, are easily detectable by either ESI-MS or ELSD-methods that should allow us to monitor the reaction by LC–MS analysis. $Sc(OTf)_3$ and $Yb(OTf)_3$ were examined as LAs (Table 1, entries 1 and 2) due to their proven activity in the above mentioned amino amidines synthesis. We also paid attention to silicon Lewis acids (SLA), whose ability to activate the C=O and C=N bonds for an interaction with C-nucleophiles is well documented.[27,28] Thus, TBDMS-OTf and TBDMS-Cl as well as TMSCl were selected as potential promoters of this reaction (Table 1, entries 3–8). Considering the fact that the combination of SLA with $Yb(OTf)_3$ is able to promote the reaction of azomethynes with π-C-nucleophiles much more effectively than these Lewis acids by themselves,[29–31] we also examined the system TBDMSOTf/$Yb(OTf)_3$ (Table 1, entry 6). Finally, two more experiments, with Brønsted acid (Table 1, HCl, entry 9) and with no additives (Table 1, entry 10), were attempted.

All evaluated additives demonstrated reactivity in the investigated MCR. However, the HCl-promoted reaction produced a mixture of several non-identified by-products that made isolation of target compound **15** problematic. TBDMS-OTf and metal triflates showed moderate activity, whereas silyl chlorides proved to be less suitable as catalysts. In contrast, the system TBDMS-OTf/$Yb(OTf)_3$ demonstrated the best catalytic activity. However, employment of 1 equiv of TMSCl as a promoter is the condition of choice because it generates the highest yield of target compound **15**[32] with no side reactions. In contrast to metal triflates, TMSCl is inexpensive—an important consideration for scale-up syntheses. Moreover, utilization of metal-free conditions avoids residual metal contamination—an important consideration for medicinal chemistry.[33–35]

The discovered conditions were further verified for ethylenediamine **5a** in MCR with benzylisocyanide and both, 4-isopropylbenzaldehyde **6b** and tetrahydropyra-

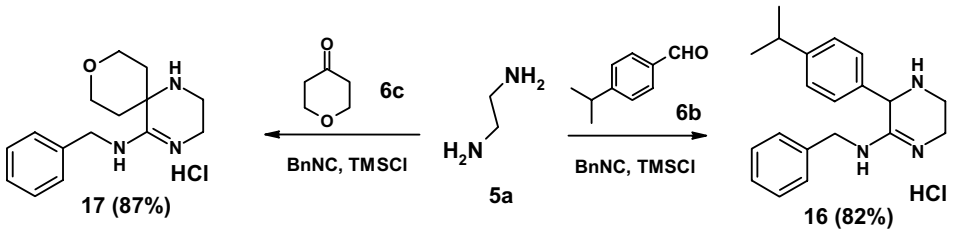
Table 1. MCR of *trans*-cyclohexane-1,2-diamine **5b**, 1-benzyl-piperidone-4 **6a**, and *tert*-BuNC **11a** in the presence of LAs[a]



Entry	Promoter (LA)	Mol %	Yield,[b] %
1	$Yb(OTf)_3$	20	54
2	$Sc(OTf)_3$	20	64
3	TBDMS-OTf	20	55
4	TBDMS-Cl	20	34
5	TMSCl	20	38
6	TBDMS-OTf/$Yb(OTf)_3$	20/20	81 (55)
7	TMSCl	100	91 (78)
8	TMSCl	200	89 (67)
9	HCl (8 M solution in dioxane)	100	64
10	None	—	Traces

[a] In each entry, a mixture of 1000 μl of 0.5 M methanol solution of azomethyne (pre-prepared by azeotropic removal of water with chloroform), 500 μl of 1 M solution of **11a**, and appropriate amount of LA was stirred for 24 h at rt in capped tubes.

[b] Yields were determined by LCMS (ELSD detection) of the reaction mixtures probes. Isolated yields for successful entries are shown in parenthesis.

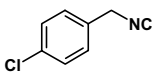
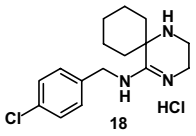
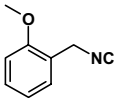
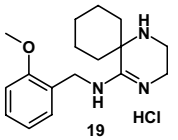
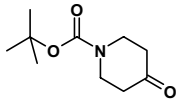
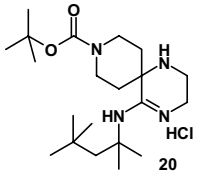
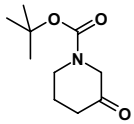
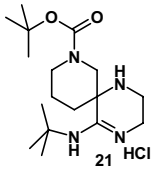
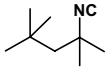
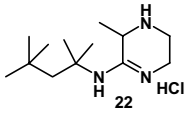
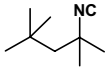
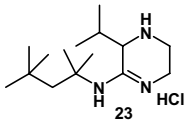


Scheme 2.

none **6c** (Scheme 2). Moreover, the series of experiments under various reaction conditions was carried out in order to optimize MCR performance.

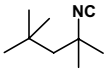
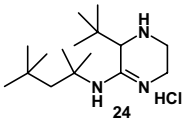
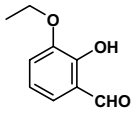
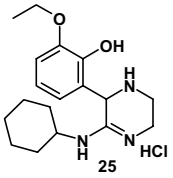
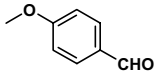
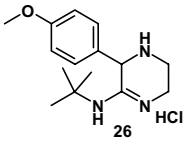
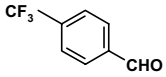
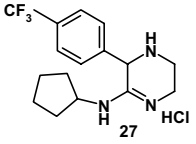
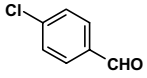
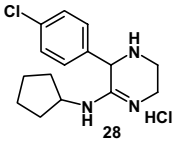
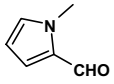
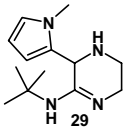
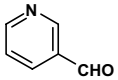
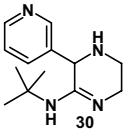
High yields of target aminopyrazines **16** and **17**[36] were achieved in both the cases. Although aprotic solvents such as chloroform or acetonitrile are known to be preferable for SLA-promoted reaction performance, they proved to be inefficient because of the formation of insoluble ethylenediamine or intermediate azomethynes salts. This reduced the reaction rate and caused the formation of several high molecular weight by-products. In contrast, alcohols and especially methanol demonstrated the best results. Furthermore, water produced during azomethyne formation did not interfere with the MCR process, and its removal is not necessary unless it might be required for azomethyne formation of low reactive carbonyl compounds. Work-up procedures were simple, chromatography-free, and allowed to isolate target materials with high degree of purity. The resulting solid colorless compounds proved to be monohydrochlorides of target aminopyrazines **16** and **17**, which existed in the N(1)-protonated forms (based on their ^{1}H NMR spectra).

Table 2. Synthesis of various 3,4,5,6-terahydropyperazine-2-amines via IMCR of ethylenediamine

Entry	Carbonyl compound	Isocyanide	Product	Yield (%)
1			 18	85
2			 19	68
3			 20	67
4			 21	63
5			 22	58
6			 23	80

(*continued on next page*)

Table 2 (*continued*)

Entry	Carbonyl compound	Isocyanide	Product	Yield (%)
7			 **24**	85
8			 **25**	58
9			 **26**	85
10			 **27**	92
11			 **28**	88
12			 **29**	58
13			 **30**	51

The scope of this MCR was examined using a variety of isocyanides and carbonyl compounds including ketones, aliphatic, aromatic, and heteroaromatic aldehydes. It was found that both, electron rich and electron poor aldehydes reacted smoothly as well as sterically hindered dimethylpropionic aldehyde or easily enolized acetaldehyde. Representative examples of 2-aminotetrahydropyrazines isolated as hydrochlorides or free bases (as it shown) are depicted in Table 2.

While the influence of additional functionalities on the reaction process is still under investigation, it appears that they have limited or no effect. For example, an *o*-hydroxy-group in 2-hydroxy-3-ethoxybenzaldehyde does not affect the reaction success (compound **28**). Therefore, additional functionalities in carbonyl and/or isocyanide components as well as secondary amino-group N(4)–H can serve to introduce additional point of diversity in the scaffolds obtainable by this MCR.

In conclusion, we report a novel TMSCl-promoted multicomponent reaction of ethylenediamine(s) with carbonyl compounds and isocyanides that leads to the variety of unique highly functionalized scaffolds with 3,4,5,6-tetrahydropyrazin-2-amine core. These scaffolds are open for further transformation due to an already existing secondary amino-group in their structures.

Scaffold diversity can be extended by a variety of components bearing additional functionalities and/or by modifications of the 2-aminopyrazine core including its oxidation up to full aromatization and/or transformations of amidine moiety. The potential of various 1,2- and 1,3-diamines in the developed MCR and its applications are currently under study in our laboratories.

Supplementary data

Detailed experimental procedures designed for parallel and scale-up synthesis of pyrazin-2-amines **15**–**30** and their spectral data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.044.

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32. (4a′*S*,8a′*S*)(4a′*R*,8a′*R*)-1-Benzyl-*N*-(*tert*-butyl)-4a′,5′,6′,7′,8′,8a′-hexahydro-1′*H*-spiro[piperidine-4,2′-quinoxalin]-3′-amine (**15**). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.28–7.36 (m, 5H); 3.61 (br s, 1H, exch. D_2O); 3.51 (s, 2H); 2.60–2.77 (m, 3H); 2.37–2.47 (m, 1H); 2.23–2.32 (m 1H); 1.95–2.11 (m, 3H); 1.69–1.79 (m, 5H); 1.46–1.54 (m, 1H); 1.31 (s, 9H); 0.97–1.40 (m, 4H); 0.84 (d, $J = 8.8$ Hz, 1H, exch. D_2O). ^{13}C NMR APT (100 MHz, $CDCl_3$): δ (ppm) 159.2 (C); 138.3 (C); 129.6 (CH); 128.5 (CH); 127.3 (CH); 63.7 (CH_2); 62.0 (CH); 53.9 (C); 53.5 (CH); 51.0 (CH_2); 48.8 (CH_2); 41.5 (C); 37.4 (CH_2); 35.1 (CH_2); 33.2 (CH_2); 32.7 (CH_2); 29.4 (CH_3); 26.0 (CH_2); 25.8 (CH_2). HRMS (ESI-TOF): calculated for $C_{23}H_{36}N_4$ ($M+H^+$) 369.3013; found, 369.3015.
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36. *General procedure for the synthesis of 3,4,5,6-tetrahydropyrazin-2-amines* **16**–**30**. The syntheses were performed in 10-ml tubes with screw caps in a one-pot manner without employment of any protective procedures such as inert or anhydrous atmosphere. A mixture of 500 μl of 1 M methanol solutions of each, carbonyl compound (0.5 mmol) and ethylenediamine (0.5 mmol) was stirred for 1 h. Solutions of trimethylchlorosilane (500 μl of 1 M, 0.5 mmol) in acetonitrile and isocyanide (500 μl of 1 M, 0.5 mmol) in methanol were added, the resulting mixture was stirred at 50–60 °C for 1 h and then at ambient temperature overnight. Reaction mixture was evaporated under reduced pressure, treated with dry EtOAc, kept in ultrasonic bath until precipitate formation was complete, then centrifuged. The precipitate was washed twice with EtOAc, acetonitrile, and Et_2O with centrifugation each time, and dried under reduced pressure yielding target compounds as monohydrochlorides. Compounds **29** and **30** were obtained as free bases employing standard procedures. Satisfactory analytical data were obtained for the synthesized compounds. The following are spectral data of representative compounds **16** and **17**.
N-Benzyl-3-(4-isopropylphenyl)-3,4,5,6-tetrahydro-pyrazin-2-amine hydrochloride (**16**): Yield 82%. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.43 (br s, 1H, exch. D_2O); 9.63 (br m, 1H, exch. D_2O); 7.28–7.40 (m, 5H); 7.24 (d, $J = 8.4$ Hz, 2H); 7.21 (d, $J = 8.4$ Hz, 2H); 4.91 (s, 1H); 4.68 (dd, $J = 15.0$ Hz, $J = 5.9$ Hz; with D_2O: d, $J = 15.0$ Hz); 4.55 (dd, $J = 15.0$ Hz, $J = 5.1$ Hz; with D_2O: d, $J = 15.0$ Hz); 3.23–3.39 (m, 2H); 2.79–2.94 (m, 2H), 2.67–2.78 (m, 1H); 1.18 (d, $J = 7.0$ Hz, 6H). ^{13}C NMR APT (100 MHz, DMSO-d_6): δ (ppm) 163.0 (C); 148.8 (C); 136.5 (C); 136.2 (C); 129.1 (CH); 128.9 (CH); 128.7 (CH); 127.0 (CH); 57.1 (CH); 45.3 (CH_2); 41.0 (CH_2); 37.1 (CH_2); 33.8 (CH); 24.5 (CH_3). HRMS (ESI-TOF): calculated for $C_{20}H_{25}N_3$ ($M+H^+$) 308.2121; found, 308.2123.
N-Benzyl-9-oxa-1,4-diazaspiro[5.5]undec-4-en-5-amine hydrochloride (**17**). Yield 87%. ^{1}H NMR (400 MHz,

DMSO-d_6): δ (ppm) 9.94 (br s(m?), 1H, exch. D_2O); 9.74 (br s (m?), 1H, exch. D_2O); 7.24–7.40 (m, 5H); 4.59 (d, $J = 3.3$ Hz, 2H; with D_2O: s, 2H); 3.68–3.78 (m, 2H); 3.59–3.67 (m, 2H); 3.18–3.25 (m, 2H; with D_2O: t, $J = 4.8$ Hz, 2H); 2.84–2.92 (m, 2H; with D_2O: t, $J = 4.8$ Hz, 2H);2.65 (t, $J = 7.3$ Hz, 1H, exch. D_2O); 2.11–2.21 (m, 2H); 1.65–1.73 (m, 2H). ^{13}C NMR APT (100 MHz, DMSO-d_6): δ (ppm) 167.1 (C); 136.3 (C); 129.2 (CH); 128.2 (CH); 127.9 (CH); 62.1 (CH_2); 53.9 (C); 44.5 (CH_2); 41.6 (CH_2); 36.2 (CH_2); 33.3 (CH_2). HRMS (ESI-TOF): calculated for $C_{15}H_{21}N_3O$ ($M+H^+$) 260.1757, found 260.1755. For detailed spectral data of the rest synthesized compounds see Supplementary data.