Tetrahedron Letters 54 (2013) 761–764

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A simple one-pot method for the mercuric oxide mediated synthesis of piperazines via oxidative diamination of olefins

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ARTICLE INFO

Article history:
Received 27 July 2012
Revised 8 November 2012
Accepted 11 November 2012
Available online 1 December 2012

Keywords:
Piperazine derivatives
Mercuric oxide
Tetrafluoroboric acid
Oxidative diamination
Ethylene diamine
Olefins

ABSTRACT

Mercuric oxide mediated one-pot synthesis of substituted piperazines via oxidative diamination of olefins with N-protected ethylene diamine has been reported. Among the various conditions tried, mercuric(II)oxide/tetrafluoroboric acid gave good to excellent yields of the desired products. A series of piperazines have been synthesized and characterized by NMR and mass spectroscopy methods.

The substituted piperazine scaffold is considered to be a privileged structure in medicinal chemistry and is widely present in the bio-active molecules of many therapeutic areas viz anti-inflammatory, antibacterial, antimalarial, anticonvulsant, antipyretic, antitumor, anthelmintic, analgesic, antidepressant, antifungal, antitubercular, anticancer, antidiabetic etc.[1–12] Moreover, in drug discovery hit to lead optimization programs, piperazine moieties have been utilized for the p*K* optimization of many leads.[13–15] Piperazine ring gives inherent rigidity to two hydrogen bond participants and lends itself well to binding within biological systems.[16] Additionally, this structural rigidity has led to the use of piperazines as ligands in asymmetric catalysis.[17] Since this privileged scaffold occurs regularly in complex natural products, a plethora of synthetic methods have been reported in the literature for their synthesis.[18–20] Moreover, in recent years, more than ten different strategies based on multicomponent reactions (MCRs) have also been published for their synthesis.[21] In spite of many synthetic strategies for the synthesis of piperazine and its derivatives, there is a need for the development of an effective and simple synthetic method for the synthesis of piperazines. An attractive strategy for the synthesis of piperazines is the oxidative diamination of olefins. This strategy was first developed by Bäckvall in 1975 for the synthesis of small heterocyclic compounds.[22] Afterward, this strategy was highly exploited for the synthesis of many heterocyclic compounds.[23] Various metal catalysts based on palladium, nickel, gold as well as stoichiometric copper reagents have been successfully employed.[24] As per our literature survey, this strategy is still not exploited for the synthesis of piperazine and its derivatives. One reason could be because most of the diamination reactions (catalyzed by above mentioned catalysts) required tethered amine[25] (amine having electron-withdrawing group). Meantime in our literature survey, we found that mercuric salts have also been utilized for the oxyamination as well as diamination reaction with simple amines for the generation of heterocyclic moiety, but still not explored for the synthesis of piperazine and its derivatives.[26] In this direction, we hypothesized that mercuric salts could be explored for the oxidative diamination addition of suitable diamine to alkenes and subsequently we successfully developed a mercuric oxide mediated one-pot synthetic method for the generation of piperazines via oxidative diamination of olefins with N-protected ethylene diamine.

Initially, we selected various mercuric salts such as $Hg(OAc)_2$, $HgCl_2$, HgO, and HgI without or with acids such as perchloric acid, boron trifluoride·etherate, and tetrafluoroboric acid to test the idea and started this study by the reaction of styrene **1a** with benzyl-protected ethylenediamine **2a** (all the results are summarized in Table 1).

During our study, THF was used as a solvent. The reaction of styrene **1a** with *N,N′*-dibenzylethylenediamine **2a** in the presence of various mercury salts gave only a minor quantity of desired product **3a** (Table 1, entries a–d). Among these conditions, mercuric acetate and mercuric oxide gave 10% and 11% of the desired product **3a** respectively. This indicates that mercuric salts could

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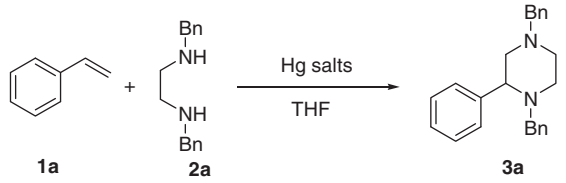
http://dx.doi.org/10.1016/j.tetlet.2012.11.110

Table 1
Effect of various mercury salts on the synthesis of piperazines via oxidative diamination of olefins

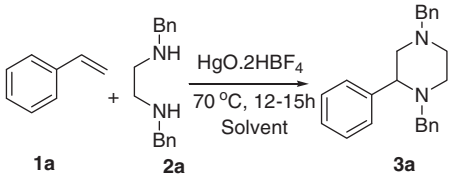


1a 2a 3a

Entry	Catalyst	Temp	Time (h)	Yield[a] (%)
a[b]	$Hg(OAc)_2$	rt-70	10	10
b[b]	$HgCl_2$	rt-70	10	5
c[b]	HgI	rt-70	10	0
d[b]	HgO	rt-70	10	11
e[c]	$Hg(OAc)_2/BF_3{\cdot}Et_2O$	rt-70	14	15
f[c]	$Hg(OAc)_2/HClO_4$	rt-70	14	25
g[c]	$Hg(OAc)_2/HBF_4$	rt-70	12	50
h[c]	$HgO/BF_3{\cdot}Et_2O$	rt-70	12	45
i[c]	HgO/HBF_4	rt-70	12	60
j[d]	**$HgO{\cdot}2HBF_4$**	**70**	12	**70**

[a] Isolated yield.
[b] Reaction conditions: Styrene **1a** (1 mmol), *N*,*N*′-dibenzylethylenediamine **2a** (1.5 mmol), Hg salt (1 mmol).
[c] Reaction conditions: Styrene **1a** (1 mmol), *N*,*N*′-dibenzylethylenediamine **2a** (1.5 mmol), Hg salt (1 mmol), rt followed by addition of acid (1 mmol).
[d] Reaction conditions: Styrene **1a** (1 mmol), *N*,*N*′-dibenzylethylenediamine **2a** (1.5 mmol), preformed $HgO{\cdot}2HBF_4$ (1 mmol).

Table 2
Effect of different solvents on the synthesis of piperazines via oxidative diamination of olefins



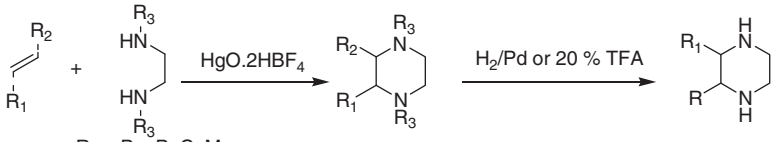
1a 2a 3a

Entry	Solvents[a]	Conversion (%)
a	Dioxane	67
b[b]	Et_2O	10
c	*t*-BME	65
d[b]	CH_2Cl_2	Traces
e	MeOH	0
f	DMF	20
g	Toluene	10

[a] Reaction conditions otherwise unless noted: Styrene **1a** (1 mmol), *N*,*N*′-dibenzylethylenediamine **2a** (1.5 mmol), preformed $HgO{\cdot}2HBF_4$ (1 mmol).
[b] Reactions performed under reflux conditions.

be utilized for oxidative diamination but needed further optimization for this conversion to get quantitative yield of the desired product. Barluenga et al. have reported that mercuric salt in the presence of perchloric acid and tetrafluoroboric acid successfully catalyzed the diamination of olefins.[26] Keeping these findings in mind, we tried the reaction of styrene **1a** with **2a** in the presence of mercuric acetate and acids such as perchloric acid, boron trifluoride·etherate, and tetrafluoroboric acid (Table 1, entries e–g) and among these conditions, mercuric acetate and tetrafluoroboric acid increases the yield of the desired product **3a** from 10% to 50%. Mercuric oxide in the presence of tetrafluoroboric acid further improved the yield of the desired product **3a** (Table 1, entry i). From this finding, it could be visualized that the addition of tetrafluoroboric acid significantly increases the yield, which might have made β-aminomercury(II) intermediate **3a** more labile and thus, very easily replaced by second nucleophile. Further, addition of preformed $HgO{\cdot}2HBF_4$ reagent (prepared by the known method)[26]

Table 3
Mercuric oxide/tetrafluoroboric acid mediated reaction of alkene with protected ethylene diamine for the generation of piperazines



1 2 3 4

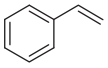
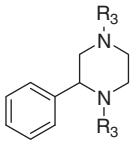
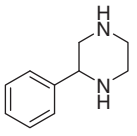
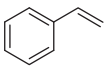
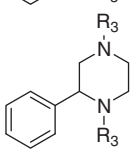
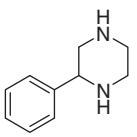
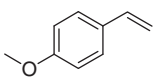
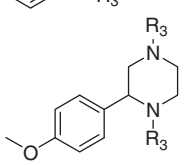
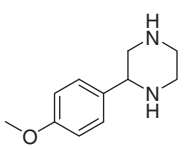
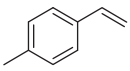
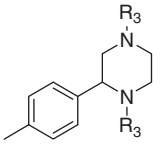
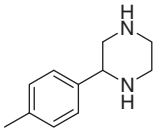
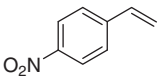
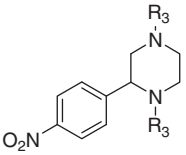
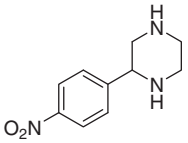
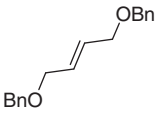
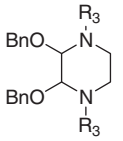
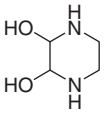
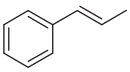
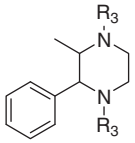
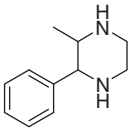
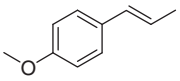
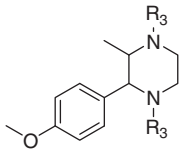
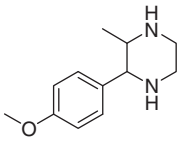
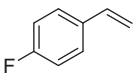
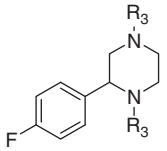
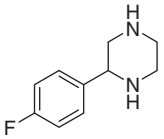
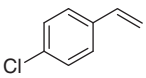
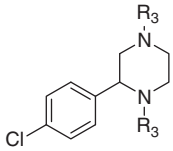
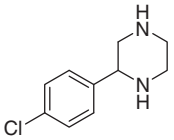
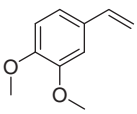
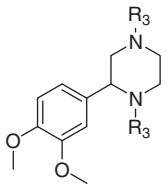
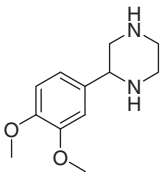
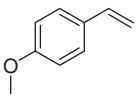
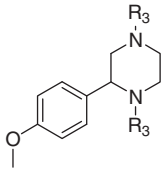
Entry	1	2	Time (h)	Yields[a] (%)	3	4	Yields[b] (%)
a		 R_3= Bn	7	70			85
b		 R_3= Boc	6	80			85
c		 R_3= Bn	6	75			90

Table 3 (*continued*)

Entry	1	2	Time (h)	Yields[a] (%)	3	4	Yields[b] (%)
d		 R_3= Bn	7	73			87
e		 R_3= Bn	7	76			45
f		 R_3= Bn	12	72			75
g		 R_3= Bn	16	60			80
h		 R_3= Bn	14	62			82
i		 R_3= Bn	8	70			89
j		 R_3= Bn	7	72			82
k		 R_3= Bn	7	73			88
l		 R_3= Me	7	77			

[a] Isolated yields of **3.**

[b] Isolated yields of **4**. Reaction condition: **1** (1 mmol), *N,N′*-disubstituted ethylenediamine **2** (1.5 mmol), $HgO{\cdot}2HBF_4$ (1 mmol) in THF at 70 °C.[30] Products were characterized by NMR and Mass spectroscopy of their respective de-protected piperazine derivatives which are in agreement with the literature reported value.[29]

yielded comparatively better yield of desired product **3a** (Table 1, entry j). The optimization results suggested that 1 equiv of $HgO{\cdot}2HBF_4$ is the best condition for the oxidative diamination of olefins with diamines. In addition to this, the effect of various solvents on the oxidative diamination of olefins with diamines was also studied and the results are summarized in Table 2. When the reactions were performed in other etherate solvents such as dioxane, diethyl ether, and *ter*-butylmethyl ether (*t*-BME), 2-phenylpiperazine derivative was formed in 67%, 10%, and 65%, respectively (Table 2, entries a–c). The use of dichloromethane gave traces of the desired product **3a** as observed on TLC (Table 2, entry d). Replacement with other solvents such as methanol, DMF, and toluene also affected the formation of the desired product **3a** drastically (Table 2, entries e–g). The present method works well in etherate based solvents, whereas in other solvents, lower yield of the desired piperazine product was obtained.

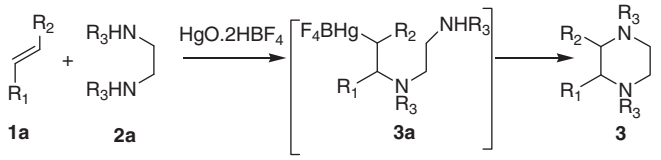


Figure 1. Plausible mechanism for $HgO{\cdot}2HBF_4$ mediated synthesis of piperazines.

In order to see the diversity of this method, various symmetrical and unsymmetrical alkenes as well as differently substituted ethylene diamines have been tried under the optimized conditions and the results are summarized in Table 3. These results showed that there is no influence of the group present on the aromatic ring of alkene (substituted styrene) toward the formation of piperazines. There is very little effect of protected group present on the N-atom of ethylene diamine. Boc-protected amines gave comparatively better yield as compared to benzyl protected ethylene diamines along with a minor quantity of Boc-deprotected product. Both electron-donating group (Table 3, entries c–d and k–l) and electron-withdrawing group (Table 3, entries e, i–j) bearing styrene underwent a coupling reaction smoothly and gave protected piperazine derivatives in good to excellent yields. Further, electron-withdrawing group bearing styrene gave comparatively better yield. The disubstituted alkene such as benzyl protected (*E*)-but-2-ene-1,4-diol also underwent the coupling reaction and gave corresponding piperazine in good yield (Table 3, entry f). Further, other di-substituted alkenes such as phenyl-2-propene and anethole also underwent diamination and gave the desired piperazine product in a good yield (Table 3, entries g and h).

All the benzyl substituted piperazines prepared under the present method were subjected to hydrogenolysis in the presence of H_2/Pd/C, which gave corresponding piperazines **4** in quantitative yield[27] and Boc-protected piperazine was also subjected to deprotection of Boc group with 20% TFA (Table 3).[28] All the protected **3a**–**h** as well as de-protected piperazine derivatives **4a**–**h** were characterized by NMR and mass spectroscopy and by comparison with literature reported data.[29] The plausible mechanism of this reaction can be visualized as, the reaction of $HgO{\cdot}2HBF_4$ with alkene **1a** followed by the attack of amino group of **2a** to generate the intermediate β-aminomercury(II)tetrafluoroborate **3a**, which undergoes an intra-molecular cyclization by the attack of second amino group of ethylenediamine to generate piperazine **3** (Fig. 1).

In conclusion, a simple one-pot high yielding method was developed for the synthesis of substituted piperazines via oxidative diamination of olefins with N-protected ethylene diamine. Both monosubstituted and di-substituted alkenes were successfully employed for the coupling reaction. Further exploration of the full scope of these reactions and its extension to oxyamination is underway and will be reported in due course.

Acknowledgments

Authors thank the Director IIIM, Jammu for spectral, library, and other facilities. One of the authors (H.K.) thanks the University of Jammu for awarding research fellowship.

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30. *General procedure for the synthesis of piperazines.* Olefins **1** (1 mmol) were dissolved in dry THF (15 mL) under N_2 and $HgO{\cdot}2HBF_4$ (1.1 mmol) was added portionwise followed by the addition of *N*,*N*′-disubstitutedethylene diamine **2** (1.5 mmol). The reaction mixture was stirred at 70 °C for the appropriate time as shown in Table 1. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography on silica gel to afford corresponding protected piperazine derivatives **3**. The compound **3** was dissolved in MeOH (9 mL) containing acetic acid (1 mL) and then added Pd/C.[27] The reaction mixture was stirred for 4 h under H_2 on a Parr hydrogenator and the progress of the reaction was monitored on TLC. After completion of reaction, the catalyst was filtered off and the organic mixture was evaporated in a rota-vapour. The crude mixture was purified by column chromatography using chloroform:methanol (95:5–80:20) as eluting mixture to get the corresponding product **4**. The products reported herein, were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The spectroscopic data of the compounds are in agreement with those reported in the literature.[29] Spectral data for **3a**[29a–d]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92–2.14 (m, 4H), 2.14–2.66 (m, 2H), 3.82 (s, 4H), 4.14 (m, 1H), 7.01–7.49 (m, 15H); ^{13}C NMR: δ 29.4, 36.5, 41.4, 62.5, 125.80, 127.40, 128.41, 144.70; MS (ESI): 342 (M^+).