Practical Method for Parallel Synthesis of Diversely Substituted 1-Phenylpiperazines

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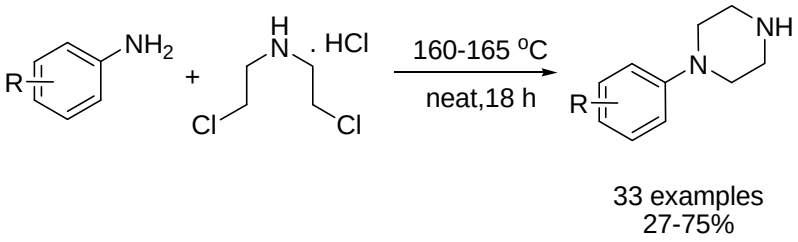

A simple and practical method to prepare ‘libraries’ of substituted 1-phenylpiperazine building blocks in parallel format have been developed.

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Igor Konstantinov,[a] Konstantin Bukhryakov,[a] Yuri Gezentsvey[a] and Mikhail Krasavin* [a, b, §]

[a] *Chemical Diversity Research Institute, 2a Rabochaya St., Khimki, Moscow Reg., 141400, Russia*

[b] *Science and Education Center "Innovative Research", Yaroslavl State Pedagogical University, 150000, Russia*

*Corresponding author, e-mail: myk@chemdiv.com, phone: +7(495)995-4944, fax: +7(495)626-9780.

[§] Current address: Eskitis Institute, Griffith University, Brisbane, QLD 4111 Australia.

Abstract

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Keywords: N-arylpiperazines, bis-alkylation, nitrogen mustard, parallel synthesis, solvent-free synthesis

INTRODUCTION

1-Arylpiperazines constitute an important class of structural motifs in CNS drug discovery. Compounds based on the privileged [1] 1-arylpiperazine scaffold have been reported, to mention a few examples, as melanocortin MC4 receptor agonists [2], serotonin 5-HT_{1A} receptor antagonists [3], dopamine D_2 receptors modulators [4].

In the course of a lead optimization program conducted in our laboratories, we recently required a rapid access to a large set of diversely substituted 1-phenylpiperazines to explore structure-activity relationships (SAR) via variations in the active compound's periphery. While hundreds of these secondary amine building blocks can potentially be acquired via commercial sources, certain SAR-informative 1-phenylpiperazines need to be synthesized from the respective (usually more available) anilines.

Several methods to convert anilines into the respective 1-phenylpiperazines appeared in the literature, typically employing 2-chloro-*N*-(2-chloroethyl)ethanamine (used as hydrochloride [5] or in an alkoxycarbonyl-protected form [6]) as a five-atom synthon to form the piperazine cycle. In some cases, the more reactive bromide counterpart of this reagent was used [7] or the reaction was conducted in the presence of an iodide salt to catalyze the process [8]. As a more benign alternative to the 'nitrogen mustard'-type reagents, 2,2'-iminodiethanol [9] or morpholine [10] could be used.

For our needs, however, we required a general and practical method that would allow preparing dozens of the requisite 1-arylpiperazines as 'libraries' of building blocks, in parallel format. Having attempted the existing literature methods to this end and found them to lack the desired practicality, we developed an alternative method to convert anilines into substituted 1-phenylpiperazines that we disclose herein.

RESULTS AND DISCUSSION

For each of the parallel reactions (Scheme 1), a 10 mL vial equipped with a magnetic stirrer was charged with an aniline (**1**, 7.6 mmol) and 2-chloro-*N*-(2-chloroethyl)ethanamine hydrochloride (**2**, 8.4 mmol). The dry solids were thoroughly mixed, each vial was capped with a pierced septum (to allow the gas evolution) and placed in a room-temperature oil bath. The temperature of the bath was raised to 160-165 °C over 30 min. The solids melted and slow evolution of the hydrogen chloride gas was observed over the next 1-2 hours. The reaction mixtures were kept at that temperature overnight and then were cooled down to room temperature. The glass-like reaction mixtures were treated with acetone (5 mL) and placed on a 45 °C ultrasonic bath for 3-4 h. The resulting fine solids were filtered off, each placed in a 100 mL round-bottomed flask and stirred with 3M aqueous sodium hydroxide solution (10 mL) and ether (60 mL). The biphasic mixtures were filtered; the organic layers were separated, washed with water (3 x 15 mL), dried over anhydrous Na_2SO_4, filtered, and treated with 4M solution of HCl in dioxane. The resulting precipitates were collected by filtration, washed with cold acetone and air-dried. The crude 1-phenylpiprazines **3** were crystallized from methanol to provide analytically pure compounds [11] in moderate to good yields (Table 1).

The scope of this method is quite general with respect to substituted anilines. The method is practically simple and can potentially be amended to an automated format. In a limited period of time, it allowed us to create a substantial arsenal of 1-phenylpiperazines on a scale of ~500 mg. The only limitation of this method that we have note so far is its failure to give the desired products 3 for anilines containing basic motifs as well as for some poorly reactive heteroaromatic amines (Fig. 1).

CONCLUSION

In summary, we have developed a practical method to prepare 'libraries' of medicinally important substituted 1-phenylpiperazine building blocks in parallel format. The method appears to have superior practicality to the literature methods reported hitherto.

ACKNOWLEGEMENT

This research was supported by the Federal Agency for Science and Innovation (Russian Federation Government Contract 02.740.11.0092).

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[11] Characterization data for selected compounds: **3b** – ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.22 (br s, NH + bound H_2O), 6.81 (s, 2H), 6.67 (s, 1H), 3.49 (m, 4H), 3.28 (m, 4H), 2.22 (s, 6H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 147.8, 138.5, 124.3, 115.3, 46.9, 41.8, 21.1; LC MS [M+H$^+$] *m/z* 191.4; **3i** - ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.60 (br s, NH + bound H_2O), 7.13 (t, J = 7.4 Hz, 1H), 6.68 (d, J = 7.4 Hz, 1H), 6.75-6.80 (m, 2H), 3.36 (m, 4H), 3.15 (m, 4H), 2.54 (q, J = 7.6 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 150.1, 144.6, 128.9, 119.5, 115.6, 113.4, 45.4, 42.4, 28.4, 15.6; LC MS [M+H$^+$] *m/z* 191.2; **3o** - ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.68 (br s, NH + bound H_2O), 7.21 (d, J = 6.5 Hz, 2H), 7.06 (d, J = 6.5 Hz, 2H), 3.41 (m, 4H), 3.16 (m, 4H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 1148.9, 141.4, 121.9, 120.2 (q, J_{C-F} = 190.2 Hz), 117.1, 45.4, 42.3; LC MS [M+H$^+$] *m/z* 247.2.

Scheme 1.

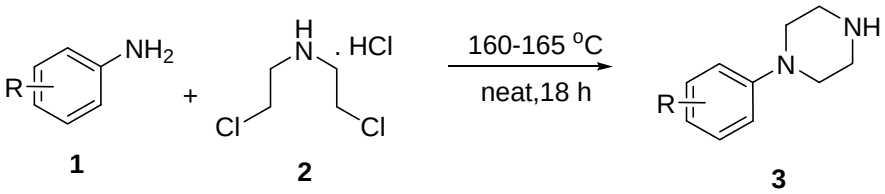


Figure 1. Examples of unreactive anilines and heteroaromatic amines.

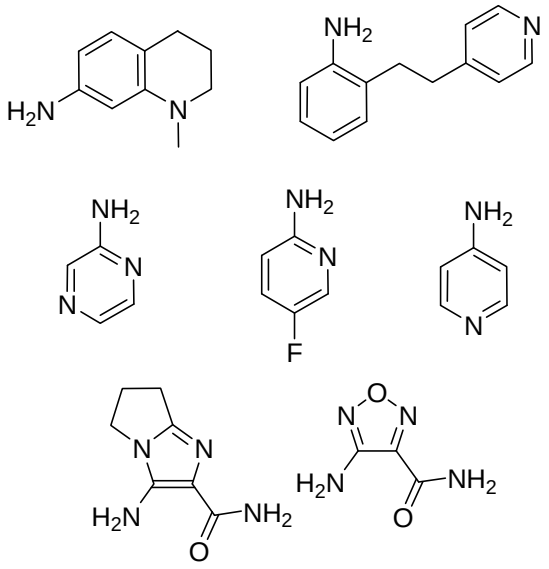
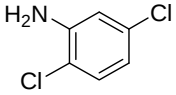
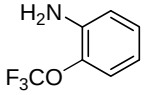
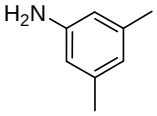
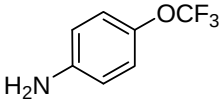
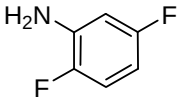
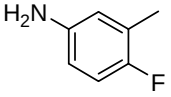
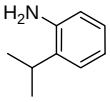
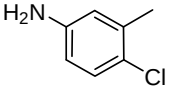
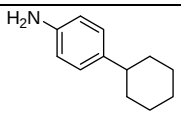
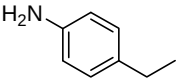
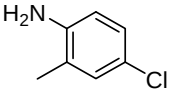
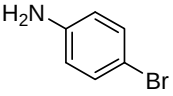
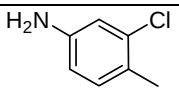
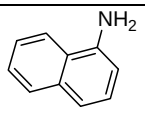
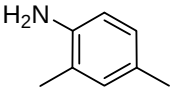
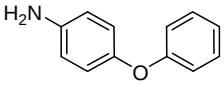
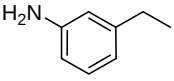
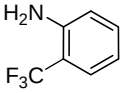
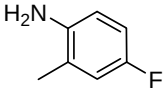
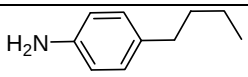
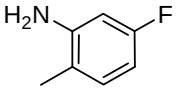
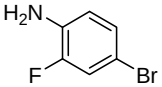
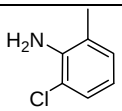
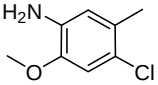
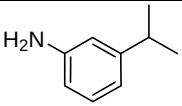
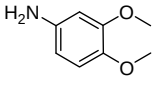


Table 1. Substituted 1-phenylpiperazines **3** synthesized in this work.

Aniline **1**	Structure	Yield of **3**, %	Aniline **1**	Structure	Yield of **3**, %
a		62	**n**		63
b		70	**o**		62
c		40	**p**		49
d		60	**q**		52
e		45	**r**		46
f		38	**s**		74
g		27	**t**		45
h		67	**u**		43
i		75	**v**		30
j		55	**w**		35
k		35	**x**		34
l		27	**y**		51
m		50	**z**		67