Pergamon

Tetrahedron Letters 40 (1999) 5655–5659

TETRAHEDRON LETTERS

Sequential mono-*N*-arylation of piperazine nitrogens. Part 1: A simplified method and its application to the preparation of a key *N,N'*-biaryl piperazine antifungal intermediate

Michael Hepperle, Jeffrey Eckert and Dinesh Gala *

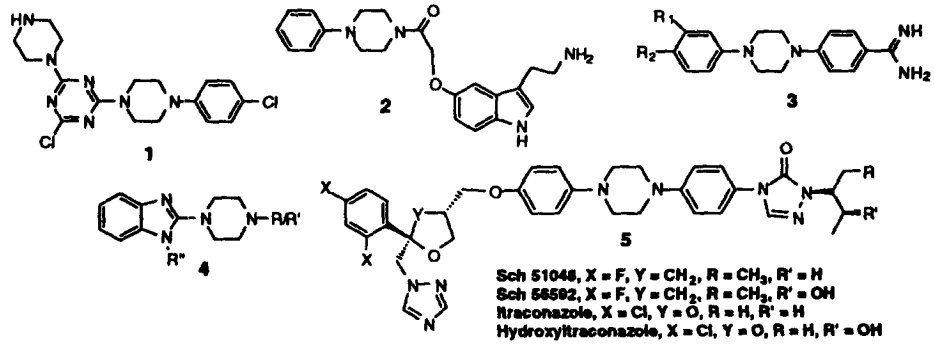
Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey, 07033, USA

Received 28 April 1999; accepted 27 May 1999

Abstract

A simple sequential *N*-arylation of piperazine without the use of a protecting group, catalyst, specialized equipment or a large excess of piperazine, and its application towards the preparation of the key differentially *N,N'*-biarylated piperazine antifungal intermediate *N*-(4-hydroxyphenyl)-*N'*-(4-aminophenyl)piperazine, **6**, is described.

Mono- and biarylated piperazines are key moieties of a variety of biologically active compounds such as cholesterol ester transfer protein inhibitors (**1**),[1] 5-HT_{1D} receptor agonists (**2**),[2] GPIIb/IIIa antagonist (**3**),[3a] serotonin-3 antagonists (**4**),[3b,c] and triazole antifungals (**5**).[4] These triazoles belong to the class of orally active broad-spectrum antifungals that contain an unsymmetrically *N,N'*-biarylated piperazine moiety. Members of this class are, for instance, Sch 51048, Sch 56592, itraconazole, and hydroxyitraconazole.[4b,c]



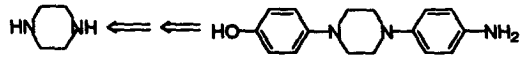
Classical synthetic routes to these differentially *N,N'*-biaryl substituted piperazines encompass the reaction of anilines with carcinogenic bis(2-chloroethyl)amine directly,[5–7] or generated in situ from

* Corresponding author.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01103-X

diethanolamine,[8,9] or ethylene oxide plus ammonia under high pressure/temperature and specialized catalyst conditions[10] to the monoaryl substituted piperazines which are then reacted with appropriate aryl halides as described below. Alternatively, these differentially substituted piperazines are made via an S_NAr reaction of piperazine with aryl halides containing electron-withdrawing groups. The S_NAr reaction requires a large excess of piperazine and harsh reaction conditions[11] or protection of one of the two nucleophilic nitrogens, usually as a carbamate, to avoid a mixture of mono-, di-, and unsubstituted piperazines which require chromatographic purifications.[12–15] Selective arylation of one nitrogen of piperazine at a time under mild laboratory conditions could overcome issues associated with the above preparations.

During the development work towards a novel, more practical and scaleable synthesis of the common intermediate **6** (Scheme 1) of the above triazole based antifungals, from commercially available chemicals, we observed that when 1.0 equivalent of either 4-bromo- or 4-chloronitrobenzene in dimethylsulfoxide (DMSO) was heated to 120°C for 12 h with 1.3 equivalents of piperazine, 1.5 equivalents of potassium carbonate, and 0.01 equivalent of tetra-*N*-butylammonium iodide (TBAI), only one piperazine nitrogen displaced the halide leading to 1-(4-nitrophenyl)piperazine **14**. After extractive acid–base work-up and without chromatographic purification, isolated yields consistently over 90% were achieved for this reaction. The same reactions worked fairly well without the use of TBAI as a phase transfer catalyst, with a 10–15% lower yield. No *N,N′*-biarylated piperazine could be detected in these reactions.



Scheme 1.

Further experiments showed that the reactivity of the aromatic halides towards piperazine (Table 1) depended on the electron density of the aromatic ring. Electron rich aromatic halide **11** does not react under these conditions. The yields for compounds **14** to **17** directly reflect the electron-withdrawing influences of the aromatic rings of the substrates **7–12**, respectively. Again, none of the *N,N′*-biarylated products were observed during the preparation of **14–17**. Interestingly, all deliberate attempts to arylate both piperazine nitrogens with 4-chloronitrobenzene either in one flask or in two separate steps with a large excess of aryl halide and/or extended reaction times, did not form the symmetrically *N,N′*-biaryl substituted piperazine **21**. A potential protonation of the secondary nitrogen of piperazine before the second arylation was ruled out by running a control experiment with 10 equivalents of base for an extended time. This experiment again yielded only compound **14** and none of **21**.

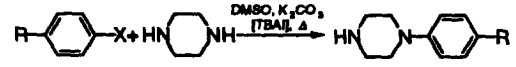
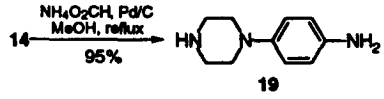


Table 1
Mono-*N*-arylated piperazines

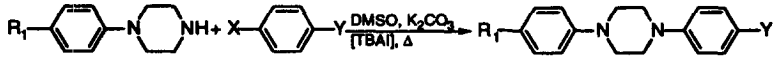
Compound	R	X	Product (Yield)[a]
7	NO_2	Br	14 (98)
8	NO_2	Cl	14 (91)
9	NO_2	NO_2	14 (76)[b]
10	CN	Cl	15 (80)
11	COMe	Cl	16 (49)
12	OMe	Br	17 (0)
13	[c]	Cl	18 (45)[d]

[a] isolated yield. [b] Without TBAI. [c] N-benzyl-2-chloro-benzimidazole. [d] See note with ref. 3c.



Scheme 2.

An electron relay theory[16] was postulated to explain the apparent lack of *N'*-arylation of the above *N*-arylpiperazines for the preparation of *N,N'*-biaryl substituted piperazines. Based on this theory the following strategy was undertaken to facilitate *N'*-arylation of *N*-aryl substituted piperazines. When compound **14** was reduced to 1-(4-aminophenyl)piperazine **19** (Scheme 2), the more basic piperazine nitrogen of **19** underwent a facile *N'*-arylation with either 4-bromo- or 4-chloronitrobenzene under the above conditions to form **23** in good yields (Table 2). By extending this theory, we discovered that, in general, *N'*-arylation proceeded fairly well if the *N*-arylpiperazine contained either an electron-donating group (**19** and **20**) or a moderately strong electron-withdrawing group (**15** and **16**). With the strong electron-withdrawing nitro group in the *para* position, as in **14**, the second arylation failed. This was confirmed by the following observations: (i) compound **21** was not formed when piperazine was exposed to an excess of 4-chloronitrobenzene under the above conditions, and (ii) compound **22**, can be formed by the reaction of **15** with 4-chloronitrobenzene but not by the reaction of **13** with 4-chlorobenzonitrile. Also consistent with the electron relay theory, the *o*-nitro group of **31** readily facilitated the *N'*-arylation to form compound **32**.[16]



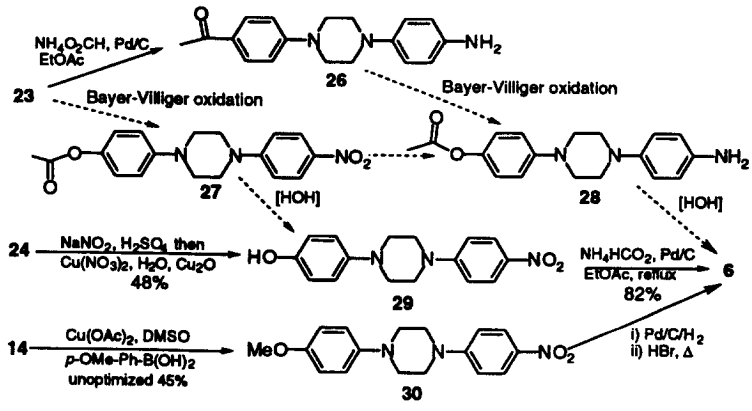
14-16,19,20 **21-25**

Table 2
N'-Arylation of *N*-aryl piperazines

Compound	R_1	X	Y	Product (yield)[a]
14	NO_2	Cl	NO_2	21 (0)
14	NO_2	Cl	CN	22 (0)
15	CN	Cl	NO_2	22 (81)
16	COMe	Cl	NO_2	23 (76)
19	NH_2	Br	NO_2	24 (85)
19	NH_2	Cl	NO_2	24 (77)
20[b]	OMe	Br	NO_2	25 (77)

[a] isolated yield. [b] available from Janssen Chimica.

As for the synthesis of the key *N,N'*-heteroaryl piperazine antifungal intermediate **6**, our initial strategy to convert **23** into **6** (outlined in Scheme 3) encountered difficulties at the Bayer-Villiger oxidation step. Under the conditions investigated (acidic to basic pH; for CF_3CO_3H, CH_3CO_3H, *m*-CPBA, or H_2O_2; with or without catalyst), essentially no desired reaction was seen with either the nitrophenyl piperazine **23** or the aminophenyl piperazine **26**. Two alternate approaches were successful, however. In the first approach, the nitroaniline **24** was diazotized and converted to the nitrophenol **29**, in situ, by the use of copper salts in aqueous solution.[17] This approach was not optimized for the preparation of **29**. Compound **29** was readily reduced to the desired intermediate **6**. In the second approach, which was based on mechanistic considerations,[16] compound **14** was arylated to **30** with a readily available copper catalyst in DMSO.[18] Although the crude yields were high, difficulty in the purification led to an isolated yield of 45%. This was then converted into **6** as shown in Scheme 3. Compounds **29**, **30** and **6** thus prepared were indistinguishable from the ones obtained via alternate chemical routes. The use of **6** via a selective *O*-alkylation in the presence of amine for the preparation of triazolone antifungals has been described elsewhere.[19]



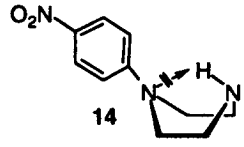
Scheme 3.

In summary, a new, simple, synthetic method for the sequential mono-*N*-arylation of piperazine nitrogens from commercially available inexpensive raw materials without the use of protecting groups, high pressure/temperature equipment, chromatographic purification or specialized metal catalysis has been developed and applied to the preparation of a key differentially *N,N'*-biaryl substituted piperazine antifungal intermediate. A mechanism for mono-*N*-arylation of unprotected piperazines has been proposed.

References

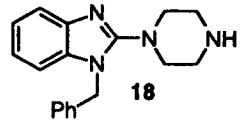
1. Xia, Y.; Mirzai, B.; Chackamannil, S.; Czarniecki, M.; Wang, S.; Clemmons, A.; Ahn, H.-S.; Boykow, G. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 919.
2. Perez, M.; Fourrier, C.; Sigogneau, I.; Pauwels, P. J.; Palmier, C.; John, G. W.; Valentin, J.-P.; Halazy, S. *J. Med. Chem.* **1995**, *38*, 3602.
3. (a) van Maarseveen, J. H.; den Hartog, J. A. J.; Tipker, K.; Reinders, J.-H.; Brakkee, J.; Schon, U.; Kehrbach, W.; Kruse, C. G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1531; (b) Morreale, A.; Galvez-Ruano, E.; Iriepa-Canalda, I.; Boyd, D. B. *J. Med. Chem.* **1998**, *41*, 2029; (c) Orjales, A.; Mosquera, R.; Labeaga, L.; Rodes, R. *J. Med. Chem.* **1997**, *40*, 586. Compound **18** represents **7** of Ref. 3c. A small amount of bis arylation was seen for **18**. The crude reaction was high yielding, unoptimized isolation procedure caused lower isolated yields of **18**.
4. (a) Heeres, J.; Backx, L. J. J.; VanCutsem, J. *J. Med. Chem.* **1984**, *27*, 894; (b) Saksena, A. K.; Girijvallabhan, V. M.; Wang, H.; Liu, Y.-T.; Pike, R. E.; Ganguly, A. K. *Tetrahedron Lett.* **1996**, *37*, 5657; (c) Tanoury, G. J.; Senanayake, C. H.; Hett, R.; Kuhn, A. M.; Kessler, D. W.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 6845.
5. Jaisinghani, H. G.; Khadilkar, B. M. *Tetrahedron Lett.* **1997**, *38*, 6875.
6. Reitz, A. B.; McDonnell, M. E.; Baxter, E. W.; Codd, E. E.; Wu, W.-N. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1927.
7. Mishani, E.; Dence, C. S.; McCarthy, T. J.; Welch, M. J. *Tetrahedron Lett.* **1996**, *37*, 319.
8. (a) Pollard, C. B.; Wicker, T. J. *J. Am. Chem. Soc.* **1954**, *76*, 1853; (b) Pollard, C. B.; MacDowell, L. G. *J. Am. Chem. Soc.* **1934**, *56*, 2199.
9. (a) JP-09255671 (Konica Chem KK); 1997; (b) Budai, Z.; Galambos, T.; Mezei, T.; Reiter, J. Humg. Pat. 91-1601: CA: 119 (15): 160318p; (c) Schroeder, W.; Ruider, G. Eur. Pat. 91-103485; CA 115 (21): 232295w.
10. (a) Bartulin, J.; Zuniga, C.; Retamal, *J. Bol. Soc. Chil. Quim.* **1982**, *27*, 144 [CA *97*:55773]. In some cases the use of alkyl/arylamine in place of ammonia results in moderate yields of differentially *N,N'* substituted piperazines; (b) Perez, M.; Potier, P.; Halazy, S. *Tetrahedron Lett.* **1996**, *37*, 8487.
11. Bent, R. L.; Dessloch, J. C.; Dunnebier, F. C.; Fassett, D. W.; Glass, D. B.; James, T. H.; Julian, D. B.; Ruby, W. R.; Snell, J. M.; Sterner, J. H.; Thirtle, J. R.; Vittum, P. W.; Weissberger, A. *J. Am. Chem. Soc.* **1951**, *73*, 3100.
12. Stewart, H. W.; Turner, R. J.; Denton, J. J.; Kushner, S.; Brancone, W. L.; McEwen, W. L.; Hewitt, R. I.; Subbarow, Y. *J. Org. Chem.* **1948**, *13*, 134.
13. Neuville, L.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 4091.
14. (a) Goldman, L.; Williams, J. H. *J. Org. Chem.* **1953**, *18*, 815; (b) Swain, A. P.; Naegele, S. K. *J. Am. Chem. Soc.* **1954**, *76*, 5091.

15. Baltzly, R.; Buck, J. S.; Lorz, E.; Schon, W. *J. Am. Chem. Soc.* **1944**, *66*, 2631.
16. As a working hypothesis, it was postulated that in compounds such as **14**, *N'*-arylation is difficult due to a diminished nucleophilicity of the 2°-amine nitrogen, resulting from a lack of participation of the arylated nitrogen in hydrogen bonding (electron relay, or charge stabilization) as shown below. *N'*-Arylation was improved by either: (i) electron donating groups on the aryl group (e.g. **19** and **20**); (ii) weaker (than NO_2) electron withdrawing groups on the aryl group (e.g. **15** and **16**); (iii) improving the hydrogen bonding capacity as shown in the following article in this issue (Eckert, J.; Chan, T.-M.; Gala, D. *Tetrahedron Lett.* **1999**, *40*, 5661); or (iv) by enhancing the electrophilicity of the reacting species, as in the case of formation of **30** (via metal catalysis).



14

17. Cohen, T.; Dietz Jr., A. G.; Miser, J. R. *J. Org. Chem.* **1977**, *42*, 2053.
18. Similar arylations of nitrogen containing compounds were recently reported (see Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933); however, this is the first example of a piperazine derivative. Also, the use of DMSO as solvent was contraindicated in the reference, but for our example, it was the best solvent used.
19. Andrews, D. R.; Gala, D.; Gosteli, J.; Gunter, F.; Mergelsberg, I.; Sudhakar, A. US Patent 5 625 064: Process for the Preparation of Triazolones, April 29, 1997.



18