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Sequential mono-*N*-arylation of piperazine nitrogens. Part 2: The role of hydrogen bonding

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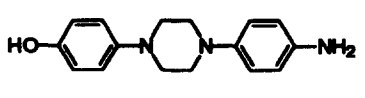
Abstract

A mechanistic study of the simple sequential *N*-arylation of piperazine suggests that in an electron-withdrawing group (EWG) containing *N*-arylated piperazines, hydrogen bonding of the secondary amine hydrogen is important for its non-metal catalyzed conversion to *N,N'*-diaryl piperazines. A combination of synthetic experiments, molecular modeling, and NMR studies were carried out to test this hypothesis.

During the investigation towards the preparation of unsymmetrical *N,N'*-diarylated piperazine **1**,[1] an entity common to the azole antifungals **2**,[2,3] we noticed an unexpected mono-*N*-arylation of piperazine, which is described in the preceeding paper. Based on a hydrogen bonding (alternately it may also be called charge stabilization, or electron relay) mechanism postulated to explain this mono-*N*-arylation of piperazine, an appropriate sequence of reactions was undertaken that secured the syntheses of **1**. Intrigued by this observation, and in view of the importance of the differentially *N,N'*-diarylated piperazines,[4–8] we investigated the validity of the above hypothesis. This manuscript describes the results of this study that support the above hypothesis.



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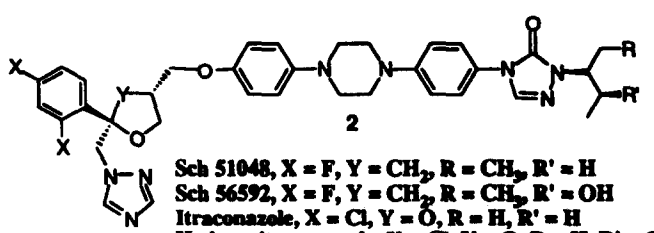

2

Sch 51048, X = F, Y = CH_2, R = CH_3, R' = H
Sch 56592, X = F, Y = CH_2, R = CH_3, R' = OH
Itraconazole, X = Cl, Y = O, R = H, R' = H
Hydroxyitraconazole, X = Cl, Y = O, R = H, R' = OH

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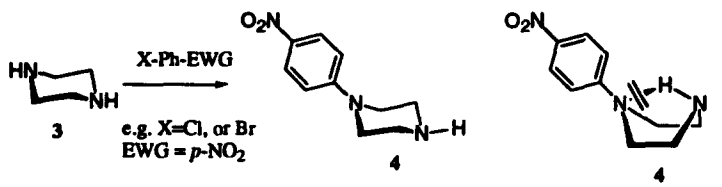
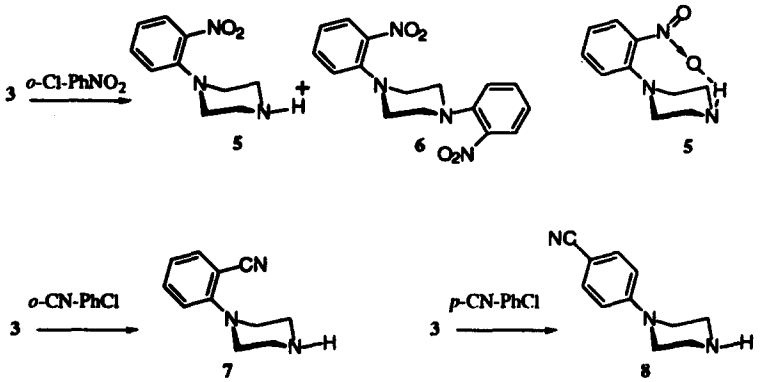
Reaction of piperazine (3) with *p*-halobenzenes containing electron-withdrawing groups (EWG=nitro, cyano, ketones; halogen=Cl, Br) led to only the mono-*N*-aryl piperazines as illustrated by the preparation of 4 in Scheme 1.[9] At the time it was hypothesized that the strongly electron withdrawing group reduced the electron density at the arylated nitrogen atom, which in turn eliminated the hydrogen bonding of the 2°-amine hydrogen, a factor necessary to improve the nucleophilicity of the 2°-amine nitrogen for its arylation. This lack of hydrogen bonding is depicted in Scheme 1. The use of electron-donating groups (e.g. methoxy or amine group) in the aromatic ring in place of the nitro group enhanced this hydrogen bonding, and allowed for the second arylation.



Scheme 1. Reaction of piperazine with halobenzenes: no hydrogen bonding

Alternatively, it was realized that even with the strongly electron-withdrawing group on the aromatic ring the nucleophilicity of the non-arylated amine nitrogen of piperazine could be enhanced by a different hydrogen bond, provided the electron-withdrawing group was in the proper position. In fact, the reaction of piperazine with *o*-nitrochlorobenzene under standard reaction conditions[9] allowed for such a hydrogen bonding as it produced a mixture of the *N*-arylated and *N,N'*-bisarylated piperazines, **5** and **6**, in 48% and 49% molar yields, respectively (Scheme 2). The models of **5** suggested the hydrogen bonding was possible via the nine-membered ring (discussed later), which allowed for the needed increase in the nucleophilicity of the secondary nitrogen atom leading to **6**.



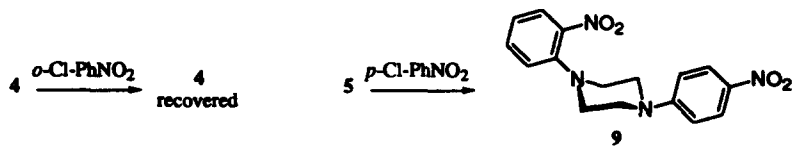
Scheme 2. Reaction of piperazine with halobenzenes: the role of hydrogen bonding

To further support this theory, it was recognized that a cyano group in place of the nitro group of **5** could not participate in such hydrogen bonding, and hence should lead to only the corresponding mono-*N*-arylated piperazine. As shown in Scheme 2, the reaction of **3** with *o*-cyano chlorobenzene led to only mono-*N*-arylated product **7** (35% isolated yield, remainder being *o*-CNPhCl).

During the course of this work, it was noticed that the reaction of *p*-$ClPhNO_2$ with **3** required about 18 hours at 100°C to form only **4**, whereas the reaction of *o*-$ClPhNO_2$ with **3** was complete in about 8 hours, and led to **5** and **6**. Since the starting materials and the products were fully soluble in DMSO in the above cases, it ruled out the possibility that the differences in the rate of reactions as well as the formation of mono-, versus mono- plus di-arylated products, were due to different solubilities/availabilities of the reactants. In the preceding paper it was shown that **4** can be made to undergo *N'*-arylation by employing

more electrophilic reagents. Thus a possibility remained that the differences in the rates as well as the products profile of these halobenzenes could be due to the enhanced electrophilicity of the latter.

To investigate this possibility, cross-over experiments, as outlined in Scheme 3, were conducted. The reaction of **4** with *o*-ClPhNO$_2$ for 7 days at 100–110°C led to no new product. This fact suggests that the latter is not significantly more electrophilic than *p*-ClPhNO$_2$ to cause *N'*-arylation of **4**. More importantly, the reaction of **5** (100–110°C, 3 days) with *p*-ClPhNO$_2$ (a electrophile which is incapable of *N'*-arylation of **4**) led to a 46% isolated yield of **9**. These results clearly underscore the importance of hydrogen bonding for *N'*-arylation of *N*-aryl piperazines.



Scheme 3. Crossover experiments

Although the synthetic work was in support of the hydrogen bonding theory, additional NMR and molecular modeling studies were undertaken to probe this theory further. For this work, compound **8** was prepared as described in the preceding paper.[1]

Carbon-13 spin-lattice relaxation time (T_1)[10] measurements were conducted for the above four mono-*N*-arylated piperazines (**4**, **5**, **7**, and **8**, 5 mg/0.6 ml in d_6-DMSO, subjected to four freeze–thaw cycles under nitrogen to remove residual oxygen in solution).[11] The results for the methylene carbons are summarized in Table 1. The effective size of the intermolecularly hydrogen bonded compounds is larger and the relaxation time is shorter compared with the intramolecularly hydrogen bonded compounds, whether in a monomeric or dimeric form. This study is particularly applicable to piperazines as they are known to associate via intermolecular hydrogen bonding.[10]

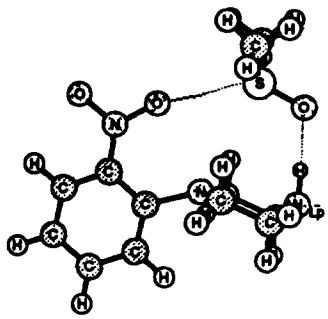
As shown in Table 1, the relaxation values for **7** and **8** are similar, and are unaffected by the substitution pattern in these compounds. On the other hand, the T_1 values for **5** are about 20 percent larger than the values for **4** consistent with the smaller size, and hence hydrogen bonding for **5**. Thus the T_1 measurements provided additional evidence for our hypothesis.

The MM2 calculation on **5** suggested that for the nine-membered intramolecular hydrogen bonding the chair form of **5** was favored by about 6 kcal/mol over the boat form. Furthermore, participation by DMSO in the hydrogen bonding via an 11-membered bimolecular structure, as shown in Fig. 1, additionally lowered the energy of **5** by 9 kcal/mol. Hence, the role of solvent in this hydrogen bonding was further investigated as discussed below.

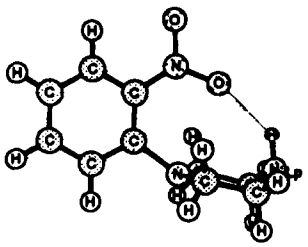
As the molecular modeling suggests, hydrogen bonding in **5** can be unimolecular or bimolecular (via solvent participation). Thus, a solvent with a diminished capacity to participate in this hydrogen bonding would allow for only the unimolecular hydrogen bonding to influence the outcome of this reaction. For this purpose three solvents for the reaction of *o*-ClPhNO$_2$ with piperazine were evaluated (Table 2).

Table 1
Spin-lattice relaxation times (T_1)

Compound	T_1
4	0.81±0.03 s, 0.91±0.03 s
5	1.06±0.01 s, 1.10±0.03 s
7	0.95±0.01 s, 1.00±0.02 s
8	0.98±0.02 s, 0.99±0.03 s



A: Hydrogen bonding in 5 via DMSO.



B: Hydrogen bonding in 5 without DMSO.

Figure 1. Molecular modeling depiction of hydrogen bonding in 5

Table 2
Solvent effect on *N*-arylation of piperazine with *o*-ClPhNO$_2$

Solvent	Temperature	Time	Ratio[c] (5:6)
DMSO	100°C	12h	1:1
NMP[a]	100°C	36h	1:1
CH_3CN	75°C	36h	2.3:1[b]
DMSO	75°C	36h	1:1[b]

a: NMP = *N*-methylpyrrolidinone. b: ~95% Reaction as judged by the consumption of *o*-Cl-Ph-NO$_2$. c: Molar ratios.

This data suggests that the solvents which can participate in H-bonding (DMSO via sulfoxide, NMP presumably via the carbonyl group) enhance bis arylation, whereas acetonitrile diminishes its contribution to the hydrogen bonding and leads to relatively more of the mono-*N*-arylated product. Again, complete solubility of **5** and **6** in acetonitrile under the experimental conditions rules out different ratios of **5** to **6** due to preferential precipitation of **5** from acetonitrile.

In summary, a series of synthetic, molecular modeling, as well as the NMR experiments, have been completed to explain a novel direct mono-*N*-arylation of piperazine. This work supports the theory that an improved nucleophilicity of the secondary nitrogen atom, attained by hydrogen bonding of the amine proton, is necessary for a direct (non-metal catalyzed) *N'*-arylation of *N*-arylpiperazines which contain electron withdrawing groups.

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9. Unless mentioned otherwise, a mixture of halobenzene, **3** (1:1.3 molar ratio; 1–10 g scale), and an excess of anhydrous K_2CO_3 were heated in DMSO at 100–110°C for 18 hours. All yields are unoptimized, isolated, and based on the halobenzenes. Satisfactory analytical data were obtained for the products.
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11. These measurements were conducted on Varian XL-400 spectrometer using the inversion recovery method at 25°C.