Pergamon

Tetrahedron Letters, Vol. 38, No. 1, pp. 63-64, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02215-0

Fragmentation of N-Boc Arylpiperazines under Basic Conditions

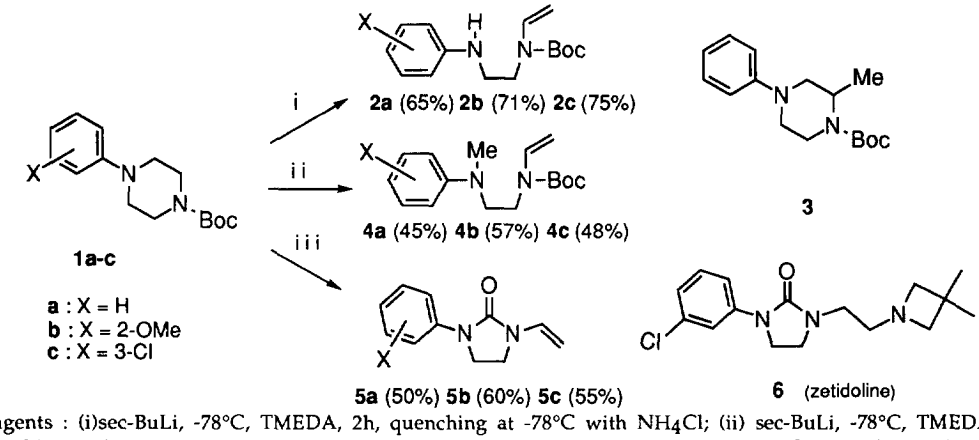
Fabrice Garrido, André Mann* and Camille-Georges Wermuth

Laboratoire de Pharmacochimie Moléculaire, Centre de Neurochimie, 5, rue Blaise Pascal, F-67084 Strasbourg France.

Abstract : N-Boc arylpiperazines **1a-c** under basic conditions (sec-Buli, TMEDA, THF) undergo ring opening fragmentation to yield arylethylenediamines **2a-c, 4a-c** at low temperature and arylimidazolidinones **5a-c** at higher temperature.

For current structure-activity studies in our laboratory, we required arylpiperazines substituted at C3.[1] As arylpiperazines are easily accessible or commercially available,[2] our first attempt was to experiment the lithiation of N-Boc phenylpiperazines, in analogy with Beak's work on the corresponding piperidines.[3] Surprisingly we observed that the transient lithiated N-Boc arylpiperazines underwent an unexpected ring fragmentation. In this letter we report our findings.

When the piperazine **1a** was treated at -78°C with sec-BuLi in the presence of TMEDA, and MeI was added as the electrophile, we observed the formation of the ring-opened compound **2a**, instead of the expected α-methylated adduct **3**. In order to explain this non anticipated fragmentation, we performed a more systematic study on the reaction conditions as well as on the diversely substituted arylpiperazines **1a-c**.

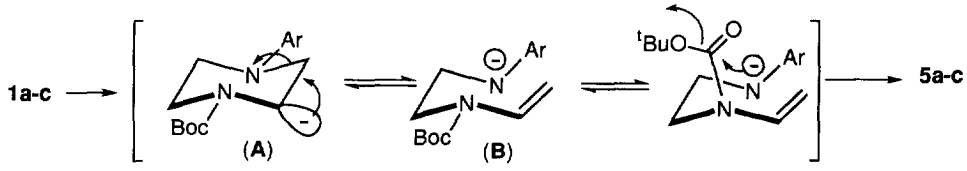


Reagents : (i)sec-BuLi, -78°C, TMEDA, 2h, quenching at -78°C with NH_4Cl; (ii) sec-BuLi, -78°C, TMEDA, 2h, quenching with excess of MeI at -78°C; (iii) sec-BuLi, -78°C, TMEDA, 2h and then -20°C, 1h and quenching with NH_4Cl at -20°C.

Scheme 1.

Under conditions (i) (1 eq. *sec*-BuLi, -78°C, THF, TMEDA, 2h, quenching at -78°C with NH_4Cl), we isolated the substituted ethylenediamines **2a-c**[4] in appreciable yield after purification by chromatography (Scheme 1); under conditions (ii) (1 eq. *sec*-BuLi, -78°C, 2h, THF, TMEDA,

quenching with excess of MeI at -78°C), we isolated the corresponding N-methylated analogues **4a-c**; finally, under conditions (iii) (1 eq. sec-BuLi, -78°C, THF, TMEDA, 2h and then -20°C, 1h and quenching with NH_4Cl at -20°C), we isolated the imidazolidinones **5a-c**[4] in respectable yields. For the ring-opening and/or ring-closing sequences, which account for the formation **2a-c**, **4a-c** and **5a-c**, we suggest the following explanation (Scheme 2). Removal of an equatorial proton from a chair like conformation of the arylpiperazine **1a-c** affords the lithiated species (**A**), stabilized by the association of the carbonyl group with lithium.[3,5] The transition state (**A**), with an anti-periplanar C-N bond, can then undergo an elimination to yield (**B**); charge stabilization on the nitrogen atom is provided by the adjacent aromatic ring.



Scheme 2.

At this stage, depending on the temperature, two reactions are possible for (**B**) : at -78°C reaction with an appropriate electrophile (H_2O or MeI) yields the arylethylenediamines **2a-c** or their corresponding methylated analogues **4a-c** respectively; at -20°C, in the absence of any electrophile, (**B**) evolves *via* an intramolecular N-carbamoylation to the arylvinyl imidazolidinones **5a-c**.

Taken together our results offer alternative routes for the preparation of substitued arylethylenediamines or arylimidazolidinones, starting from easily accessible arylpiperazines. It is noteworthy to mention that the phenylimidazolidinone, **5c** is a part of zetidoline (**6**), an atypical antidepressant (Scheme 1).[6,7]

Acknowledgment. We thank Bioprojet (Paris) for funding F. Garrido.

References and Notes

1. Sautel, F.; Griffon, N.; Sokoloff, P.; Schwartz, J. C.; Lanay, C.; P. Simon, P.; J Costentin, J.; Schoenfelder, A.; Garrido, F.; Mann, A.; Wermuth, C. G. *J. Pharm. Exp. Ther.* **1995**, *275*, 1239-1246.
2. Mishami, E.; Dence, C. S.; McCarthy, T. J.; Welch, M. J. *Tetrahedron Lett.* **1996**, *37*, 319-323.
3. Beak, P.; Lee, W. K. *Tetrahedron Lett.* **1993**, *58*, 1109-1117.
4. Selected analytical data : **2a** ^1H NMR ($CDCl_3$, 200 MHz, 50°C) δ 1.45 (s, 9H), 2.99 (s, 3H); 3.48-3.55 (m, 2H), 3,68-3,75 (m, 2H), 4.24-4.28 (d, 1H, J=9.5 Hz), 4.34-4.42 (d, 1H, J=16.0 Hz), 6.67-6.78 (m, 3H), 7.02-7.14 (dd, 1H, J=9.5 and 16.0 Hz), 7,19-7,26 (m, 2H).
5a : IR (neat) 3108-2907, 1698, 1625, 829-751. ^1H NMR($CDCl_3$, 200 MHz, 25°C) δ: 3.63-3.71 (m, 2); 3.90-4.00 (m, 2H), 4.17-4.25 (d, 1H, J=16 Hz); 4.30-4.35 (d, 1H, J=9.0 Hz), 7.05-7.15 (dd, 1H, J=16 Hz and 9 Hz), 7.33-7.40 (m, 3H), 7.57-7.62 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 38.7, 42.1, 89.9, 117.7, 123.0, 128.8, 130.3, 140.2, 153.8. MS (m/z) : 188, 160, 131, 118, 105, 91, 77.
5. Houk, K. N.; Rondeau, N. G.; Beak, P.; Zajdel, W. J.; Schleyer, P. R.; Chandrasekhar, J. *J. Org. Chem.* **1981**, *46*, 4108-4110.
6. Wright, W. B. Brabander, H. J.; Hardy, R. A.; Osterberg, A. C. *J. Med. Chem.* **1966**, *9*, 852-857.
7. Assandri, A.; Galliani, G.; Zerilli, L.; Tuan, G.; Tarzia, G., Barone, D. *Biochem. Pharmacol.* **1986**, *35*, 1459-1467.

(*Received in France* 7 *October* 1996; *accepted* 8 *November* 1996)