Tetrahedron Letters,Vol.25,No.29,pp 3067-3070,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

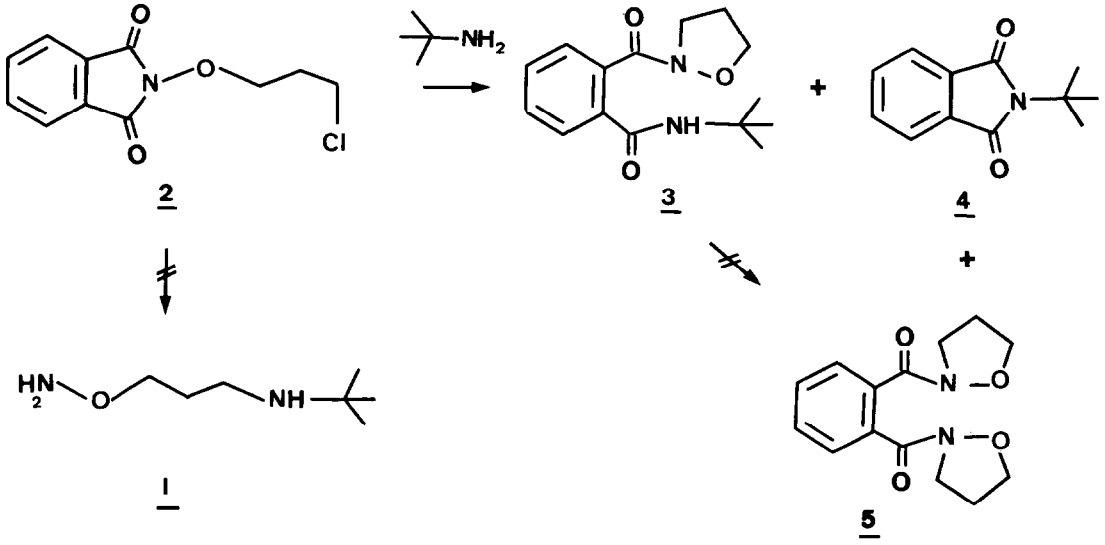
THE REACTION OF AMINES WITH PHTHALIMIDE DERIVATIVES A CONVENIENT SYNTHESIS OF ISOXAZOLIDINE

M. BOUZOUBAA and G. LECLERC*
Institut de Pharmacologie, laboratoire de Pharmacochimie (ERA 142 CNRS, U. 206 INSERM), 11 rue Humann, 67000 Strasbourg, France.

SUMMARY : The reaction of tert-butylamine, isoxazolidine and hydrazine with N-[(3-chloropropyl)oxy]phthalimide is investigated. A convenient synthesis of oxazolidine is described.

The preparation of beta-adrenergic agents [1,2] called for an efficient method of synthetising 3-(aminooxy)-N-tert-butyl-propanamine 1. N-hydroxyphthalimido ethers have recently been used to synthesize various O,N-heterocycles [3]. To extend the utility of these synthons, the action of tert-butylamine on the phthalimido ether 2 has now been explored (Scheme 1).

Scheme 1



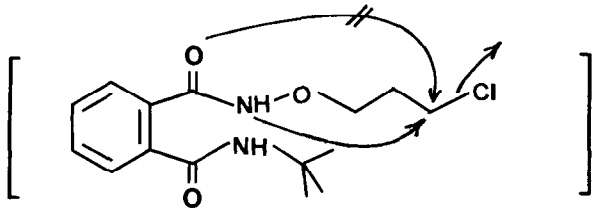
2 3 4 5 1

When performed at 100°C in a sealed tube, the reaction gave unisolable products. However, the action of 2 in the presence of a large excess of tert-butylamine at room temperature (12 h) gave a mixture of 3 (40%), 4 (30%) and

5 (30%, separated [4] by column chromatography on silica gel and eluting with a 95 : 5 mixture of EtOAc and $(Et)_3N$.

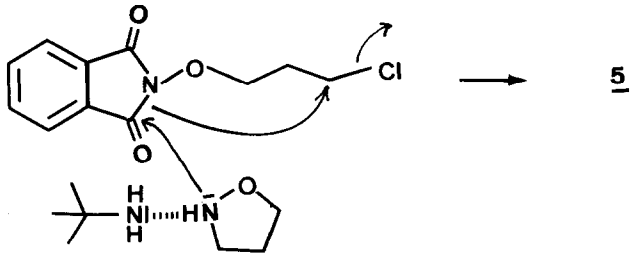
The CO-N bond of the phthalimido ethers was weakened by the presence of the electron-attracting etheral oxygen, which explains the opening by methanol (tert-butylamine catalyst needed). Therefore, 3 was thought to result from the cleavage of the phthalimido bond by tert-butylamine, followed by the intramolecular displacement of the chlorine atom by the carbamate function. In contrast with previous observations [3], the intermediate carbamate A could not be separated. Furthermore, no heterocycle resulting from an oxygen attack of the carbamate function on the ω-halogen was observed. This might indicate a concerted opening of the phthalimido ether by the amine with the simultaneous intramolecular displacement of the ω-chlorine atom. As expected, under very mild conditions (R.T.) the chlorine atom was not directly displaced by the tert-butylamine which rules out any formation of 1 from 2.

Scheme 2

A 

4 might be formed by intramolecular displacement of oxazolidine by the adjacent amide function. When the reaction depicted in Scheme 1 was monitored by TLC, only 3 appeared after 4 h. Later, this was followed by 4 and 5, in approximately the same amounts. After 12 h, a mixture of 3, 4 and 5 was obtained in a ratio of 4:3:3. The formation of the dioxazolidine derivative 5 in the presence of a large excess of tert-butylamine was particularly puzzling. The question arose whether 5 could result from 3 by displacement of the tert-butylamine group by the oxazolidine generated during the formation of 4. The preferential attack by oxazolidine was surprising in view of its reported basicity (pKa = 8.95, 25°C) [5] compared to that (10.83, 18°C) of tert-butylamine. However, the greater steric bulk of the primary amine might explain its inability to attack 2. When 3 (1 equiv.) was dissolved in ca. 10 equiv. of tert-butylamine and 1 equiv. of isoxazolidine, no 5 was formed but 4 did appear. At this point, it became obvious that 5 was derived from 2. Surprisingly, when 2 was treated with excess oxazolidine, no 5 was formed but a catalytic amount of tert-butylamine in the reaction mixture produced 5 readily : the mechanism in the formation of 5 might therefore be as follows :

Scheme 3



Similar mechanisms based on kinetic studies were proposed for the base catalysed aminolysis of esters [6,7]. The susceptibility of 2 towards various reagents led us to react it with hydrazine hydrate (1 equiv.). 1,2-oxazolidine hydrochloride was produced with excellent yields [8] (80%) by this procedure and easily separated from the insoluble phthalyl hydrazide. The best method hitherto available called for the use of hydroxylamine carbamate followed by ring closure with 1,3-dibromopropane [5,9] with a reported yield of 30%.

In summary, it appears that functionalized ethers are versatile synthons for the preparation of various heterocycles, but not for oxyamine derivatives such as 1. However, the latter compounds are easily obtained by replacing 2 with N-[(3-chloropropyl) oxy]5-norbornene-2,3 dicarboximide [3,12].

REFERENCES AND NOTES

* Author to whom correspondence should be sent.

1. LECLERC, G., BIETH, N. and SCHWARTZ, J.; J. Med. Chem. 1980, 23, 420.
2. BOUZOUBAA, M., LECLERC, G., DECKER, N., ANDERMANN, G. and SCHWARTZ, J.; J. Med. Chem. (under press).
3. AMLAIKY, N., LECLERC, G. and CARPY, A.; J. Org. Chem. 1982, 47, 517.
4. Compound 2 was prepared according to the method described for the N-[(2,3 epoxypropyl)oxy]phthalimide [3,11], mp = 71°C (MeOH). ^{1}H NMR (CCl_4), δ = 7.62 ppm (s, 4H), δ = 4.15 (t, J = 6Hz, 2H), δ = 3.65 (t, J = 6Hz, 2H) and δ = 2.02 (q, J = 6Hz, 2H). Compound 3, mp = 116°C (EtOAc), anal. calc. for $C_5H_2ON_2O_3$, ^{1}H NMR ($CDCl_3$), δ = 7.30 ppm (m, 4H), δ = 6.10 ($CDCl_3$), (broad s, 1H), δ = 3.80 (t, J = 7Hz, 2H), δ = 3.55 (t, J = 7Hz, 2H), δ = 2.12 (q, J = 7Hz, 2H) and δ = 2.18 (s, 9H), IR ($CHCl_3$) 3400 cm^{-1} (NH), 1650-1625 (-CO-NH-, -CO-NO-), MS 276 (∿2), 204 (60), 188 (44) and 147 (100). Compound 4, mp = 59-60°C (petroleum ether), anal. calc. for $C_{12}H_{13}NO_2$, ^{1}H NMR (CCl_4), δ = 7.55 ppm (s, 4H), δ = 1.55 (s, 9H). IR ($CHCl_3$)

1710-1775 cm^{-1} (-CO-N-CO-). Compound 5, mp = 136°C (EtOAc), anal. calc. for $C_{14}H_{16}N_2O_4$, ^1H NMR ($CDCl_3$) δ = 7.45 ppm (s, 2H), δ = 4.03 (t, J = 7Hz, 4H), δ = 3.75 (t, J = 7Hz, 4H) and δ = 2.30 (q, J = 7Hz, 4H) IR ($CHCl_3$) 1650 cm^{-1} (strong, -CO-NO-), MS 204 (100).

5. HINE, J. and EVANGELISTA, R.; J. Am. Chem. Soc. 1980, 102, 1649.

6. BRUICE, J.C. and FELTON, S.M.; J. Am. Chem. Soc. 1969, 91, 2799.

7. FELTON, S.M. and BRUICE, J.C.; J. Am. Chem. Soc. 1969, 91, 6721.

8. Hydrochloride isoxazolidine preparation : to a solution of N-[(3-chloro)-propanoxy]phthalimide 2 (1 g, 4.2 mmol) in 10 ml EtOH, hydrazine hydrate (0.21 g, 4.2 mmol) was added and stirred for 30 mn at R.T. The phthalyl hydrazide precipitate was filtered and EtOH was evaporated under vacuum. The isoxazolidine hydrochloride was recrystallized from MeOH-THF, mp 125-126°C (yield from hydroxyphthalimide ∿ 80%), litt. (mp 124-125°C) [5,9], oxalate salt, mp = 135°C (MeOH), anal. calc. for $C_5H_2NO_5$. ^1H NMR (D_2O), δ = 4.02, ppm (t, J = 7Hz, 2H), δ = 3.41 (t, J = 7Hz, 2H) and δ = 2.27 (q, J = 7Hz, 2H).

9. KING, H.; J. Chem. Soc. 1942, 432.

10. Oxyamine 1 was prepared according to the method described for its 2-hydroxy analogue [3] ; oxalate salt, mp = 164°C (MeOH). ^1H NMR (D_2O) δ = 3.90 ppm (t, J = 5Hz, 2H), δ = 2.90 (t, J = 5Hz, 2H), δ = 1.90 (m, 2H) and δ = 1.10 (s, 9H).

11. KLIGEL, W.; Pharmazie, 1970, 25 (7), 400.

12. FUJINO, M., KOBAYASHI, S., OBAYASHI, M., FUKUDA, T., SHINAGAWA, S. and NISHIMURA, O.; Chem. Pharm. Bull. 1974, 22 (8), 1857.

ACKNOWLEDGEMENTS

We gratefully acknowledge financial support to M. Bouzoubaa from P.O.S. Laboratories, Kaysersberg, France.

(Received in France 16 March 1984)