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A NOVEL SYNTHESIS OF 5-ACYLAMINOBENZIMIDAZOLE-2-CARBAMATES : INTRAMOLECULAR REGIOSELECTIVE ADDITION TO QUINONE-IMIDES.[1]

S. Rajappa*, R. Sreenivasan and A.V. Rane
CIBA-GEIGY Research Centre, Goregaon, Bombay 400 063, India.

Abstract : Oxidation of N',N" -biscarbomethoxy-N-(4-acylamino) phenylguanidines with lead tetraacetate has given novel 5-acylamino-benzimidazole-2-carbamates by a process involving regioselective cyclization of intermediate quinoneimides.

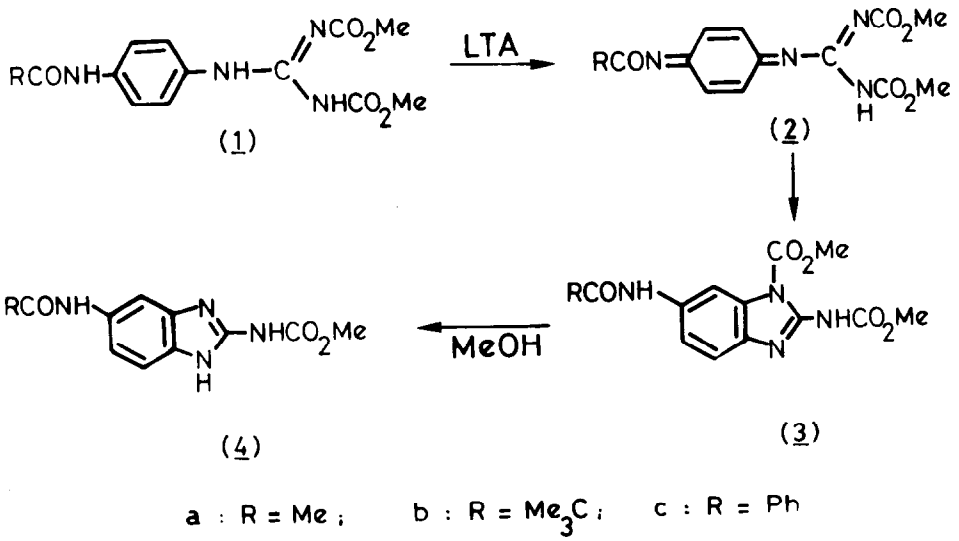
Benzimidazole-2-carbamates with specific substituents at position 5 are highly active against human and veterinary intestinal helminths[2]. The economic importance of these drugs can be gauged by the fact that the judicious use of these has reduced a potential loss of £ 160 million caused by uncontrolled parasitic nematodes in ruminants to an actual loss of only £ 30 million[2]. Until now the heterocyclic ring in such compounds has invariably been constructed from an appropriately substituted ortho-phenylenediamine (Scheme 1). We describe below a new approach to the synthesis of benzimidazole-2-carbamates bearing an acylamino group at position 5, by a process involving oxidative cyclization of 4-acylaminophenyl guanidine derivatives. The cyclization itself is regioselective and leads to products having novel substitution patterns.

The addition of external nucleophiles to quinoneimides has been well-investigated[3]. It struck us that an intramolecular attack by a suitably located nitrogen nucleophile on the quinoneimide generated in situ, could directly produce benzimidazoles. Specifically, we were interested in the conversion of N',N" -biscarbomethoxy N-(4-acylamino) phenylguanidines (1) into derivatives of benzimidazole-2-carbamates (Scheme 2).

The precursors (1) can be easily prepared from 4-nitroaniline by acylation and reduction, followed by reaction with N,N'-biscarbomethoxy-S-methylthiourea. Oxidation of these 4-acylaminophenylguanidine derivatives (1) with lead tetraacetate (LTA) in refluxing chloroform, filtration of the lead salts and evaporation of the chloroform gave the 1-carbomethoxy-benzimidazole-2-carbamates (3), still contaminated by small amounts of lead salts. The ^{1}H NMR spectra of these compounds showed the presence of two different OMe groups in the molecule.[3a ($CDCl_3$) : 3.89 and 4.17 p.p.m. 3b ($CDCl_3$) : 3.83 and 4.13 p.p.m.]. The adhering lead salts could be

Scheme 1

Scheme 2



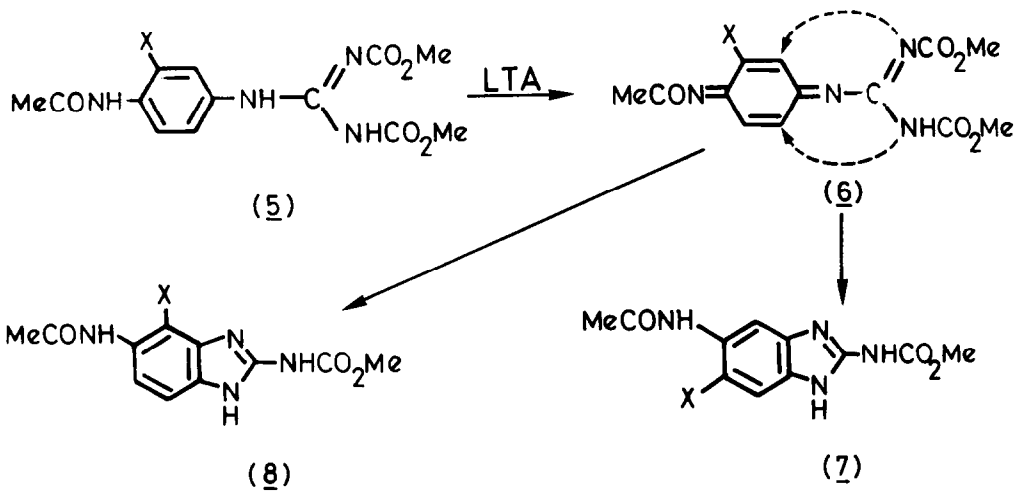
a : R = Me ; b : R = Me_3C ; c : R = Ph

eliminated by stirring the compounds for a few minutes in refluxing methanol; however, this also resulted in the removal of the ester group at position 1. The final pure products isolated were thus the 5-acylaminobenzimidazole-2-carbamates (4). The following are illustrative examples : 4a, m.p. 295–304° (d), yield 49.7%; ^{1}H NMR (TFA), 2.50 (s, Me), 4.07 (s, OMe), 7.3 to 8.2 p.p.m. (one AB quartet and one singlet, 3 Ar-H). 4c, m.p. 320–330° (d), yield 38.7%; ^{1}H NMR (TFA), 4.07 (s, OMe), 7.3 to 8.3 p.p.m. (m, 8 Ar-H). The structure of the 5-benzamido compound (4c) was confirmed by comparison with an authentic sample prepared from 2-nitro-p-phenylenediamine by a sequence outlined earlier[4].

N',N" -Biscarbomethoxy-N-4-chlorophenylguanidine was recovered unchanged after treatment with LTA under the same conditions. This proved the necessity of having a 4-acylamino group for oxidative cyclization to take place, and hence by implication, the intermediacy of a quinoneimide.

If another substituent X is present in the benzene ring, adjacent to the acylamino group, then cyclization can give rise to two products as shown in Scheme 3. The two isomers can be distinguished by their ^{1}H NMR spectra (two singlets vs an AB quartet in the aromatic region). If the quinoneimide

Scheme 3



a : X = OMe ; b : X = Me ; c : X = Cl ; d : X = CF_3.

(6) were indeed an intermediate, an electron-releasing substituent X would prevent nucleophilic attack at the site adjacent to it; cyclization would then proceed at the other available position, resulting in the formation of (7). In accordance with our expectation, when X was OMe, (7a) was formed in 24.3% yield; m.p. 280-285° (d); ^{1}H NMR (TFA), 7.33 (s, Ar-H), 8.50 p.p.m. (s, Ar-H). The other isomer (8a), if present, was below the detectable limit. Similarly when X was Me, only (7b) was obtained in 22% yield; m.p. 310-312° (d); ^{1}H NMR (TFA), 7.63 (s, Ar-H), 7.78 p.p.m. (s, Ar-H). However, when X was Cl, a mixture of (7c) and (8c) was obtained in the ratio 5:3 (total yield 47.2%) as estimated from ^{1}H NMR (TFA) : 7.83 (s), 8.37 (s), 7.63 (d, J = 9 Hz), 7.90 p.p.m. (d, J = 9 Hz).

The critical test of our hypothesis was provided by the exclusive occurrence of the sterically disfavoured vicinal cyclization when X was electron-withdrawing. Oxidation of the trifluoromethyl derivative (5d) gave (8d) as the only isolable product in 19.8% yield; m.p. 300-302° (d); ^{1}H NMR (TFA), 7.70 (d, J = 9 Hz), 8.03 p.p.m. (d, J = 9 Hz).

The reaction we have outlined is qualitatively different from those oxidative benzimidazole cyclizations in which the new bond is formed between a nucleophilic carbon and an electrophilic nitrogen terminus[5], or the ones proceeding *via* nitrene intermediates[6].

References and Notes

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