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NOVEL [1,3]-MIGRATION OF METHYL GROUP IN IMIDAZO[4,5-*c*]QUINOLINE

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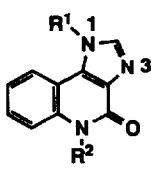
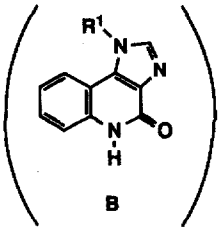
ABSTRACT: In synthetic studies of imidazo[4,5-*c*]quinolin-4(5*H*)-one derivatives, which exhibit a potent antiasthmatic activity, an unusual rearrangement was observed, where the methyl group migrates from the N-1 to the N-3 position on the imidazole during the reaction of Chapman rearrangement of 1-methyl-4-phenoxy-1*H*-imidazo[4,5-*c*]quinoline **2**.

1*H*-imidazo[4,5-*c*]quinilin-4(5*H*)-one derivatives **A** have been reported to exhibit a potent antiasthmatic activity[1]. In the synthesis of their analogues, the alkyl group (R^2) was usually introduced by the reaction of compound **B** with an appropriate alkyl halide under basic conditions. Direct arylation on the amide nitrogen of **B** was tried under a variety of conditions without success. This difficulty prompted us to develop another route. The Chapman rearrangement[2] is the thermal shift of aryl imidates to *N*,*N*-diaryl amides. We applied this rearrangement to the synthesis of the N-phenyl derivative **4** using a key intermediate **2**.

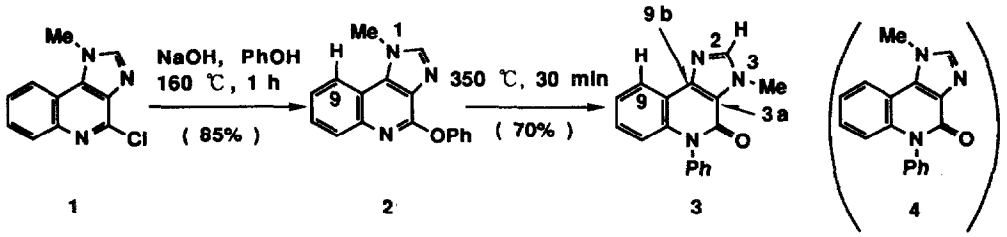


A



B

Scheme 1



1 **2** **3** **4**

As shown in Scheme 1, **2**[3] was prepared from **1**[4]. Heating of **2** at 300 ℃ under an argon atmosphere without solvent did not give any products. But the reaction occurred at 350 ℃ to afford **3**[5] instead of the expected compound **4**. The position of the methyl group in **3** was confirmed by the spectroscopic analysis[6]. The

rearrangement of the phenyl group from oxygen to nitrogen was accompanied by the migration of the methyl group on the imidazole ring from the N-1 to the N-3 position. This methyl migration in imidazole is very unusual because the thermal migration of substituents on nitrogen of imidazole generally proceeds to the carbon atoms. Begg et al.[7] have reported the rearrangement of 1-substituted imidazoles to afford mainly 2-substituted imidazoles, together with 4-substituted isomers as minor products. In the case of 1-tritylimidazoles, Gieseman et al.[8] have found that melting of 4,5-diphenyl-1-tritylimidazole or 2-phenyl-1-tritylimidazole gave 4,5-diphenyl-2-tritylimidazole or 2-phenyl-4-tritylimidazole, respectively. To our best knowledge, there have been no reports regarding the [1,3]-migration of substituents on imidazole.

The steric interaction between 1-Me and 9-H, and the cross conjugation of the double bond in imidazole with the carbonyl group can give driving forces for the rearrangment which results in the thermodynamically stable 3-substituted product **3** at a high temperature.

In conclusion, the unusual [1,3]-migration of the methyl group in the imidazole framework was observed during the Chapman rearrangement of 1-methyl-4-phenoxy-1*H*-imidazo [4,5-*c*]quinoline **2**. Mechanism of this reaction is currently under study.

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References and Notes:

1. F. Suzuki, T. Kuroda, Y. Nakasato, K. Ohmori, and H. Manabe, U.S. Patent 4 994 468, 1991.
2. (a) A. W. Chapman, *J. Chem, Soc.*, *127*, 1992 (1925). (b) D. H. Hey and T. M. Moynehan, *J. Chem. Soc. II*, 1563 (1959).
3. **2**; H^1 NMR (DMSO-d_6) δ 8.40-8.44 (m, 1H), 8.35 (s, 1H), 7.45-7.75 (m, 5H), 7.25-7.35 (m, 3H), 4.31 (s, 3H); IR (KBr) υ 1520, 1468 cm^{-1}; MS (m/e) 275 (M^+), 274; mp 201-206 ℃.
4. J. F. Gerster and W. Minn, U.S. Patent 4 689 338, 1987.
5. **3**; H^1 NMR (DMSO-d_6) δ 8.29 (s, 1H), 8.15-8.23 (m, 1H), 8.54-8.72 (m, 3H), 8.25-8.45 (m, 4H), 6.52-6.62 (m, 1H), 4.05 (s, 3H); IR (KBr) υ 1653 cm^{-1}; MS (m/e) 275 (M^+), 274; mp 245-249 ℃.
6. The observation of NOE between 3-Me and 2-H (no NOE between 3-Me and 9-H) and the long range couplings based on long range selective proton decoupling experiments ($^3J_{C9b\text{-}H(C2)}$ = 12.3 Hz and $^3J_{C3a\text{-}H(C2)}$ = 4.9 Hz) indicate that the methyl group is located as shown in formula **3** (Scheme 1).
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