Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 10, pp. 1267-1268, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)00205-9

PRACTICAL SYNTHETIC ROUTE TO BENZIMIDAZOLE-2-CARBOXYLATE DERIVATIVES VIA I_2-INDUCED OVERALL 5-*ENDO-TRIG* CYCLIZATION

Hirotaka Yukawa [a], Takeshi Nagatani [a], Yasuhiro Torisawa [b], Yoshihiko Okaichi [b], Nobuhito Tada [b], Takuya Furuta [b], Jun-ichi Minamikawa [b], and Takao Nishi [a] *

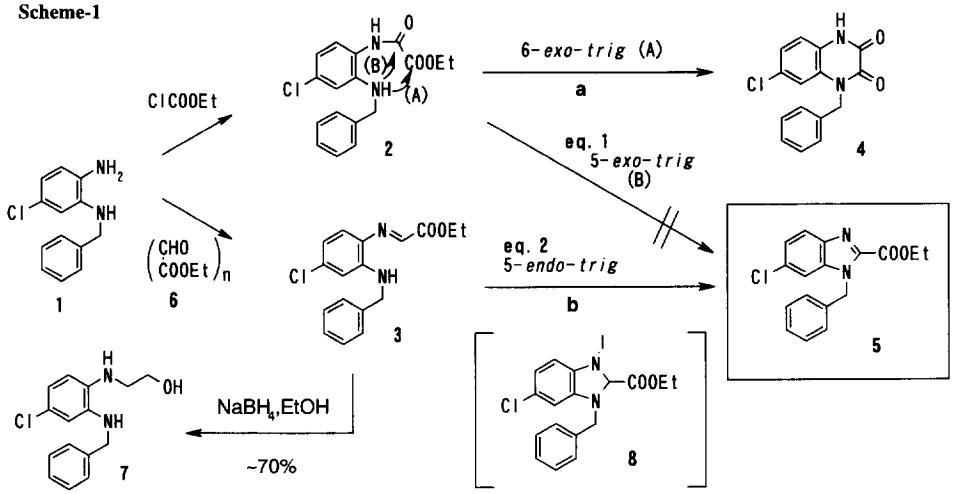
[a] *3rd Tokushima Inst. of New Drug Res., and* [b] *Process Research Laboratory, Second Tokushima Factory, Otsuka Pharmaceutical Co. Ltd., Kawauchi-cho, Tokushima, 771-01 Japan*

Abstract: A practical synthetic route for benzimidazole-2-carboxylate derivatives has been developed, in which an iodine-induced 5-endo-trig cyclization path is involved as a key step. © 1997 Elsevier Science Ltd.

The benzimidazole ring constitutes an important skeletal fragment in medicinal chemistry and hence, a variety of reports have been presented for their synthesis and biological evaluation.[1] In the course of our synthetic studies of potent inhibitors for cyclic nucleotide phosphodiesterase, a practical synthetic route to some benzimidazole-2-carboxylates such as compound (**5**) has been sought to allow multi kilo-scale production of this key intermediate. Because of the instability of the free acid, indirect methods have frequently been devised for the preparation of these carboxylate derivatives.[2] Although no direct and general protocols were available, it emerged that two simple reaction pathways could be eligible for our synthetic objective as shown in **Scheme-1**. The first choice was a 5-*exo-trig* cyclization process (eq-1) from the amide intermediate (**2**), while 5-*endo-trig* cyclization (eq 2) was another choice from the imine intermediate (**3**). Guided by the Baldwin rule, we initiated our survey according to eq-1 as a first choice. In contrast to our expectation, however, all attempts to cyclize the amide intermediate (**2**) resulted in the formation of an undesired 6-membered product (**4**) in high yield, with not even a trace of the desired 5-membered product (**5**) being detected in the reaction mixture.

Therefore, we next focused our attention on the alternative route: eq-2. Encouraged by recent literature, we attempted to perform an electrophile-induced 5-*endo-trig* cyclization,[3] which sometimes offers efficient synthetic routes to 5-membered heterocycles . We thus carefully investigated the reaction of the diamine (**1**) and ethyl glyoxylate polymer (**6**). Reaction of the diamine (**1**) with the aldehyde polymer (**6**) in EtOH at r.t. cleanly furnished the precursor imine (**3**), whose structure was confirmed by both spectroscopic means (^{1}H-NMR, IR, MS) and chemical transformation to (**7**).[4] The results of the crucial benzimidazole cyclization are briefly summarized in **Scheme-1**. The desired compound (**5**) was obtained from the imine (**3**) in EtOH in low yield via cyclization, followed by air oxidation without any catalyst. When TsOH was used as a catalyst, the product yield was increased for small scale operation, but with low reproducibility of the reaction. It was supposed that TsOH accelerated only cyclization and did not effect the oxidation process. Among the catalysts examined, I_2 in EtOH was proved to be the most effective in terms of handling, ease of work-up and reproducibility of the reaction.

Scheme-1



Conditions for cyclizations:

a) 2 to 4 : EtOH, HCl, r.t. (~quant) / EtOH, NaOEt, r.t. (~quant)

b) 3 to 5 : EtOH, r.t. (20%) / TsOH, EtOH r.t.(30~60%) / Nitrobenzene, TsOH (30%)/ I_2, EtOH, (80%)

In summary, we have disclosed here a direct and efficient synthetic procedure for the synthesis of benzimidazole-2-carboxylate derivatives, in which an iodine-induced overall 5-*endo-trig* cyclization path is involved as a key step, indicating that a *N*-iodo intermediate (**8**) might be the most plausible intermediate.

Typical experimental procedure:

To a solution of 2-benzylamino-4-chloroaniline (**1**) (10g, 43mmol) in EtOH (50ml) was added a 50% solution of ethyl glyoxylate polymer in toluene (**6**) (12.5ml, 1.5eq), and the mixture was stirred for 30 min at r.t. before a mixture of iodine (7g, 0.5 eq) in EtOH (33ml) was added at the same temperature (a slightly exothermic reaction). The resulting mixture was then stirred for 3h at r.t. before quenching with an aqueous solution of $Na_2S_2O_3$ (7g in 40ml H_2O). Stirring was continued for 1h to precipitate the product. The precipitate was collected by filtration to afford nearly pure material (**5**) (10.7g, 79%) as a faint yellow solid mass after washing with EtOH. Recrystallization from EtOAc gave pure material (**5**) as colorless needles (mp 160-161℃) with 99.5% purity judged by HPLC.

References and Notes:

1. See as recent examples for the 2-arylbenzimidazole synthesis: a) Ende, J. J. V.; Delfosse, F.; Lor, P.; Haverbeke, Y. V., *Tetrahedron*, **1995**, *51*, 5813-5818; b) Patzold, F.; Zeuner, F.; Heyer, T.; Niclas, H.-J., *Syn. Commun.*, **1992,** *22*, 281-288; c) Yadagiri, B., Lown, J. W., *ibid*, **1990**, *20*, 955-963; d) Toja, E.; Selva, D.; Schiatti, P. *J. Med. Chem.*, **1984**, *27*, 610-616.
2. See for example: Boger, D. L.; Yun, W.; Cai, H.; Han, N. *Bioorg. Med. Chem.* **1995**, *3*, 761-775.
3. Knight, D. W.; Jones, A. D., *J. Chem. Soc. Chem. Commun.*, **1996**, 915-916 and references cited therein.
4. Selected spectral data. **3**: ^{1}H-NMR (d_6 -DMSO, δ): 8.09 (1H, s, N=CH), 4.44 (2H, d, J=6.0 Hz, CH_2- Ph), 4.03 (2H, q, J=7.0 Hz, CH_2), 1.30 (3H, t, J=7.0 Hz, CH_3); **7**: ^{1}H-NMR (d_6 -DMSO, δ, ppm) 7.5 - 6.2 (8H, aromatic H), 4.29 (2H, d, J=5.8 Hz, CH_2Ph), 5.55, 4.68 (each 1H, t, J=5.8 Hz, NH), 4.73 (1H, t, J=5.8 Hz, OH), 3.63, 3.10 (each 2H, q, J=5.8Hz, CH_2), EI-Mass (m/z): 276 (M^+)

(*Received in Japan* 14 *March* 1997; *accepted* 14 *April* 1997)