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A novel and efficient iodine(III)-mediated access to 1,4-benzodiazepin-2-ones

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Abstract—A novel access to 1,4-benzodiazepin-2-ones starting from glycine and alanine derivatives is described. The key cyclization step was performed by the action of phenyliodine(III)bis(trifluoroacetate) (PIFA) on the corresponding methoxyamide derivatives leading to the C(9a)–N(1) bond construction. This strategy avoids the necessity of additional functionalization on the phenyl ring and facilitates the access to a number of 1,4-benzodiazepine derivatives. Additionally, no racemization in the cyclization step was observed starting from optically pure (*S*)-alanine ester. © 2002 Elsevier Science Ltd. All rights reserved.

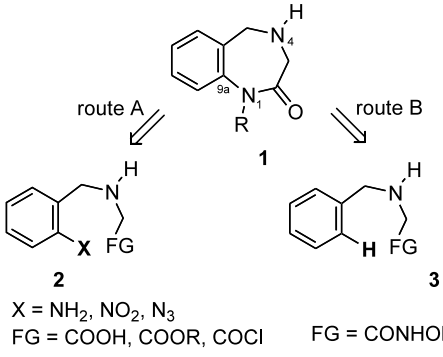
1,4-Benzodiazepine derivatives have varied biological activities and are one of the most important classes of bioavailable therapeutic agents.[1] Examples have been reported that act as anxiolytic, anticonvulsant, and antihypnotic agents,[2] selective cholecystokinin (CCK) receptor subtype A or B antagonists,[3] κ-selective opioid antagonists,[4] platelet-activating factor antagonists,[5] human immunodeficiency virus (HIV) transactivator Tat antagonists,[6] GPIIbIIIa inhibitors,[7] and reverse transcriptase inhibitors.[8] This broad biological activity is the reason for the profound attention that the scientific community has paid to the synthesis of this kind of heterocycles.[9]

In particular, most of the strategies directed toward the preparation of 1,4-benzodiazepin-2-ones of type **1** can be summarized by route A depicted in Scheme 1. They all require an aminophenyl group (or any other related nitrogen containing functional group) and a carbonyl functionality, such as COOH,[10] COOR[11] and COX,[12] as shown in precursor **2a**. This assumption may limit the access to a series of the target heterocycles with different substitution patterns on the benzene ring.

Therefore, we considered that the design of a novel access to benzodiazepine series by the construction of the C(9a)–N(1) bond on simple non-functionalized benzene rings would be most desirable. On the other hand, the projected synthesis (vide infra) will provide the 2-oxo derivatives[13] in contrast with the more widely studied benzodiazepin-2,5-diones.

In recent years, our group has been concerned with the development of hypervalent iodine reagents for the synthesis of heterocyclic compounds. The clean transformations achieved, the mild conditions employed, and the low toxicity associated with it, prompted us to include PIFA in our synthetic plans. Therefore, we have taken advantage of the known[14] ability of PIFA to generate *N*-acylnitrenium ions from *N*-alkoxyamides of type **2b** which, eventually, could be trapped intramolecularly by arene rings, as shown in Scheme 2, to afford the desired heterocycles.[15]

Because aminoacids are one of the most useful building blocks for the preparation of 1,4-benzodiazepines, we



Scheme 1. Retrosynthetic analysis for 1,4-benzodiazepin-2-ones.

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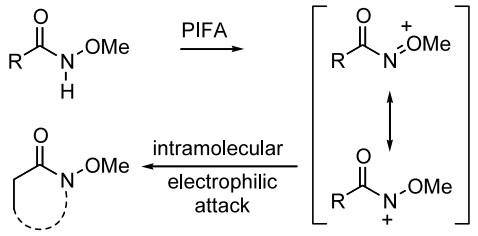
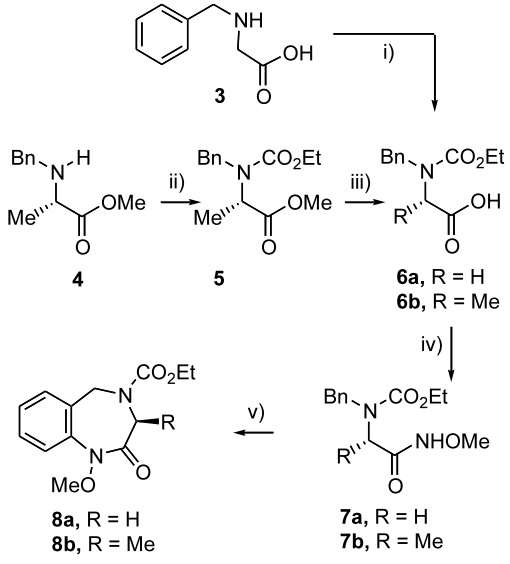


Scheme 2. Generation of the electrophilic *N*-acylnitrenium species and intramolecular attack.

employed the commercially available *N*-benzylglycine (**3**) and the known[16] *N*-benzyl-α-aminoester **4** as starting materials of our synthesis. Following the route depicted in Scheme 3, derivative **6a** was prepared directly from **3** by *N*-acylation with ethyl chloroformiate, and derivative **6b** was prepared[17] in a two-step sequence by protection of aminoester **4**[18] followed by basic hydrolysis[19] of the resulting derivative **5**.[20] After a number of assays, the optimal transformation into amides **7a**,**b** was accomplished using methoxylamine hydrochloride and a combination of EDC, HOBt and triethylamine in CH_2Cl_2.

As mentioned above, and in order to promote the key cyclization step, PIFA was selected as the source of hypervalent iodine to generate electrophilic *N*-acylnitrenium ions from amides **7a**,**b**. At this point, the action of the required additive was studied in both cases and, therefore, an optimization of the standard conditions was carried out. Cyclization of **7a** to yield benzodiazepine-2-one **8a** was best performed[21] using boron trifluoride etherate (60% yield) instead of TFA



Scheme 3. Synthesis of 1,4-benzodiazepin-2-ones **8a**,**b**. *Reagents and conditions*: (i) NaOH, ClCOOEt, THF/H_2O, rt (quantitative); (ii) NaOH, ClCOOEt, THF/H_2O, rt (98%); (iii) LiOH, THF/H_2O, rt (96%); (iv) $NH_2OMe{\cdot}HCl$, Et_3N, EDC, HOBt, CH_2Cl_2, rt (87% for **7a**; 75% for **7b**); (v) PIFA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20°C (60% for **8a**); (v) PIFA, TFA, CH_2Cl_2, 0°C (70% for **8b**).

(30% yield). Conversely, trifluoroacetic acid was the reagent of choice to transform amide **7b** into benzodiazepine-2-one **8b** (70% yield) instead of $BF_3{\cdot}OEt_2$ (30% yield). In addition, the enantiomeric excess of benzodiazepine **8b** was measured to be >98% (HPLC).[22]

In summary, a novel entry to the 1,4-benzodiazepin-2-one skeleton by a PIFA mediated intramolecular cyclization has been described. The efficiency, and lack of racemization throughout the synthesis when starting from (*S*)-alanine methyl ester, characterize the reported novel approach.

Acknowledgements

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16. Spectroscopic data of compound **4** can be found in: Szilágyi, L.; Györgydeák, Z. *J. Am. Chem. Soc.* **1979**, *101*, 427–432.
17. For an alternative synthesis of **6b** including spectroscopic information, see: Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157–6163.
18. This substrate was prepared following standard procedures by reductive amination of benzaldehyde with (*S*)-alanine methyl ester.
19. LiOH in a mixture of THF/H_2O was employed to avoid, as detected under other conditions, racemization at this stage.
20. *N*,*N*-Dibenzyl substituted precursors of type **4** were also prepared but the corresponding final cyclization step proceeded with limited success (20% yield for the corresponding *N*-benzyl-*N*-methoxy-3-methyl-1,4-benzodiazepin-2-one). This and other ancillary studies that facilitated the synthesis' achievement will be reported elsewhere.
21. **(3*S*)-4-Ethoxycarbonyl-1-methoxy-3-methyl-1,3,4,5-tetrahydro-2*H*-[1,4]benzodiazepin-2-one (8b)**: A solution of TFA (0.07 mL, 0.91 mmol) and PIFA (169 mg, 0.39 mmol) in 8 mL of CH_2Cl_2 was added at 0°C to a solution of amide **7b** (100 mg, 0.36 mmol) in 7 mL of the same solvent, and the new solution was stirred until total consumption of the starting material (tlc, Hex/EtOAc, 7/3). Then, the mixture was washed with Na_2CO_3 (10% aq.) (1×4 mL), dried over Na_2SO_4, filtered and the solvent was evaporated at reduced pressure. The resulting residue was purified by column chromatography (Hex/EtOAc, 7/3) to afford benzodiazepine **8b** as a yellowish oil (70%). ^{1}H NMR (32°C): δ 1.03 (d, J=7.0, 3H), 1.26 (t, J=7.1, 3H), 3.81 (s, 3H), 4.16 (q, J=7.1, 2H), 4.25 (d, J=14.5, 1H), 4.82 (d, J=14.5, 1H), 4.95 (q, J=7.0, 1H), 7.21–7.40 (m, 2H), 7.43–7.50 (m, 2H). ^{13}C NMR: δ 14.5, 17.4, 46.4, 57.8, 61.9, 61.9, 120.4, 127.1, 128.3, 129.4, 129.6, 138.6, 154.3, 165.7. IR (neat): ν 1698, 1683 cm^{-1}. MS (EI) m/z (%): 278 (M$^+$, 44), 250 (76), 235 (41), 220 (13), 219 (82), 135 (41), 132 (49), 130 (24), 120 (93), 106 (55), 105 (100), 104 (39). HRMS calcd for $C_{14}H_{18}N_2O_4$ 278.1255, found 278.1266. $[\alpha]_D^{20}$ −238 (*c* 0.2, CH_2Cl_2). Ee: 99% (Chiralcel OJ, Hex/EtOAc, 98/2, 0.7 mL/min, t_R = 43.35 min).
4-Ethoxycarbonyl-1-methoxy-1,3,4,5-tetrahydro-2*H*-[1,4]-benzodiazepin-2-one (8a): Compound **8a** was obtained in 60% yield from **7a** following the procedure described for **8b** but using $BF_3{\cdot}OEt_2$ instead of TFA and working at −20°C. Purification was carried out by column chromatography (Hex/EtOAc, 7/3) to afford benzodiazepine **8a** as a yellowish oil (70%). ^{1}H NMR: δ 1.26 (t, J=6.7, 3H), 3.80 (s, 3H), 4.02 (s, 2H), 4.16 (q, J=6.7, 2H), 4.54 (s, 2H), 7.28–7.37 (m, 2H), 7.42–7.52 (m, 2H). ^{13}C NMR: δ 14.5, 47.6, 48.3, 62.1, 62.5, 120.6, 127.3, 127.6, 127.7, 130.3, 138.9, 154.8, 162.7. IR (neat): ν 1698 cm^{-1}. MS (EI) m/z (%): 264 (M$^+$, 22), 236 (40), 205 (100), 177 (33), 161 (18), 133 (24), 132 (41), 120 (58), 106 (47), 105 (48), 104 (41). HRMS calcd for $C_{13}H_{16}N_2O_4$ 264.1115, found 264.1110.
22. Chiralcel OJ, Hex/^{i}PrOH (98/2), 0.7 mL/min.