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1,4-BENZODIOXIN CHEMISTRY : A NEW ROUTE TO C-3 FUNCTIONALIZED 2-METHYLENE-1,4-BENZODIOXANS

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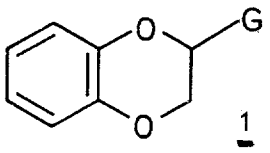
Summary : *The building-up of C-3 functionalized 2-methylene-1,4-benzodioxan structures was achieved through zinc salt-mediated Mitsunobu substitutions carried out with a 1,4-benzodioxin-2-yl carbinol.*

1,4-Benzodioxans 1 have played a prominent role in anti-hypertensive therapy as alpha-blocking agents (e.g. Prosympal, G = CH_2NEt_2 and Piperoxan, G = CH_2N⟨⟩) or as beta-blocking agents (e.g. G = $CHOH\text{-}CH_2NR_aR_b$)[1].



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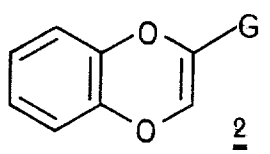


2

(a) G = CH_2OH

(b) G = CH_2I

(c) G = $CH_2NR_aR_b$

(a) G = CH_2OH (b) G = CH_2I

(c) G = $CH_2NR_aR_b$ (d) G = CH_2OAc

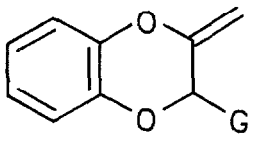
(e) G = $CH_2SCSNMe_2$ (f) G = CH_2N⟨⟩

The synthesis of their olefinic analogs 1,4-benzodioxins 2, which also display interesting pharmacological properties[2] was recently developed by Coudert et al.[3] In the course of our studies about the electrophilic activation of hydroxyl functions through a zinc salt-mediated Mitsunobu reaction,[4] we thought of interest to sketch out a smooth pathway from the hydroxyl substrates 1a and 2a to the related iodomethyl derivatives 1b and 2b - convenient precursors to the pharmacologically active amino-structures 1c and 2c.

When submitted to the reaction conditions (PPh_3, diisopropyl azodicarboxylate, zinc iodide in THF at room temperature; cf.ref.4), alcohol 1a[5] was smoothly converted

into the known[6] iodo-derivative 1b in 88% yield.

In the same conditions, 2-hydroxymethyl-1,4-benzodioxin 2a[7] showed an essentially different behaviour : after purification of the reaction mixture on a silicagel column, the fast-moving iodide 2b was isolated in very low yield[8], whereas the more polar major product(yield 72%) was identified with the hemiacetal 3a[9].



3

(a) G = OH (b) G = I

(c) G = OAc (d) G = N_3

(e) G = $SCSNMe_2$

Such a result led us to assume that the unstable iodide 3b was first formed through a major SN_2' attack at C-3 (remote from the intermediate oxyphosphonium leaving group), then hydrolyzed on silicagel during the purification step[10]. In order to check this assumption, the same reaction was performed with miscellaneous nucleophilic reagents. For instance, zinc acetate reacted with 2a to yield 65% 3c and 12% 2d[11], while zinc azide[4] led almost exclusively to 3d[12] in 75% yield. On the other hand, ziram[4] only gave the crystalline dithiocarbamate 2e[13] (77% yield; mp 91-2°C) : the rationalization of the regioselectivity based on the HSAB theory (C-3 assumed to be a softer center than C-2') for a preferred SN_2' attack was therefore questionable unless one postulates a fast sigmatropic rearrangement of the initially formed dithiocarbamate 3e to the more stable isomer 2e[14]. More experiments are now under way to try and bring answers on that particular mechanistically significant problem.

Nevertheless, the application of the zinc salt-mediated Mitsunobu substitution in the case of the 1,4-benzodioxinyl alcohol 2a provides a very smooth access to these new (to the best of our knowledge) C-3 functionalized 2-methylene-1,4-benzodioxanyl structures 3 which obviously offer a high chemical potentiality in heterocyclic synthesis[15].

As a first concrete example, the following preliminary experiment was run to try and reach one of our initially disclosed goals, i.e. the elaboration of amino-structures 2c from readily available alcohol 2a via a short and convenient route.

Thus, 2a was first reacted with zinc iodide in the modified Mitsunobu conditions (PPh_3, diisopropyl azodicarboxylate in THF at room temperature) until complete transformation of the starting material into the mixture of regio-isomers 2b and 3b was effected (TLC monitoring); excess dry piperidine was then added to the crude reaction medium and reacted smoothly at room temperature to yield (73% after work-up and silicagel column chromatography) compound 2f[16], the olefinic analog of Piperoxan.

Therefore, one may logically expect this one-pot double SN'_2 displacement to allow the straightforward elaboration of the pharmacologically useful amino-derivatives 2c from the benzodioxinyl alcohol 2a. The scope of the rearrangement as well as its synthetic versatility are now under study.

Acknowledgments

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References and notes

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3) G. Coudert, G. Guillaumet and B. Loubinoux, Tetrahedron Lett., 1059 (1978).

4) (a) P. Rollin, Synth.Commun., 16, 611 (1986)
(b) P. Rollin, Tetrahedron Lett., 27, 4169 (1986)
(c) J.R. Pougny and P. Rollin, J.Carbohydrate Chem., 5, 701 (1986).

5) We thank Dr D. Mauleon and Dr A. Delgado (Barcelona University) for a very generous gift of racemic 2-hydroxymethyl-1,4-benzodioxan.

6) C. Milani, R. Landi-Vittory and G.B. Marini-Bettolo, Rendiconti dell'Istituto superiore di sanità, 22, 207 (1959); Chem.Abstr. 54, 1522i (1960).
^{1}H NMR (300 MHz, $CDCl_3$) data : δ 6.93 (m, 4H), 4.37 (dd, $J_{3,3'}$ 11.3 Hz, $J_{3,2}$ 1.7 Hz, H-3), 4.29 (m, H-2), 4.17 (dd, $J_{3',2}$ 5.9 Hz, H-3'), 3.39 (bd, $J_{\alpha,\alpha'}$ 13.0 Hz, H-α), 3.33 (dd, $J_{\alpha',2}$ 3.3 Hz, H-α'); H_α and $H_{\alpha'}$ refer throughout to the exo-methylene site.

7) G. Coudert and G. Guillaumet, to be published.

8) Fully satisfactory spectroscopic (IR and 300 MHz ^{1}H NMR in $CDCl_3$) and analytical data were obtained for the new compounds.
2b ; ^{1}H NMR : δ 6.82 (m, 2H) and 6.64 (m, 2H), 5.99 (s, H-3), 4.06 (s, 2H, H-αα').

9) ^{1}H NMR : δ 6.94 (m, 4H), 5.70 (d, $J_{3,OH}$ 4.7 Hz, H-3), 4.79 (d, $J_{\alpha,\alpha'}$ 2.2 Hz, H-α), 4.55 (d, H-α'), 3.52 (d, OH).

10) In some experiments, the presence of remaining 3b in the 2b fast-moving chromatography fraction could be detected by ^{1}NMR.
3b ; ^{1}H NMR : δ 6.95 (m, 4H), 5.60 (s, H-3), 4.81 (d, $J_{\alpha,\alpha'}$ 2.2 Hz, H-α), 4.52(d,H-α').

11) ^{1}H NMR
3c : δ 6.96 (m, 4H), 6.70 (s, H-3), 4.88 (d, $J_{\alpha,\alpha'}$ 2.3 Hz, H-α), 4.61 (d, H-α'), 2.06 (s,3H, CH_3CO).
2d : δ 6.83 (m, 2H) and 6.66 (m, 2H), 4.45 (s, 2H, H-αα'), 2.11 (s, 3H, CH_3CO).

12) ^{1}H NMR : δ 6.98 (m, 4H), 5.83 (s, H-3), 4.89 (d, $J_{\alpha,\alpha'}$ 2.3 Hz, H-α), 4.56 (d, H-α').

13) ^{1}H NMR : δ 6.81 (m, 2H) and 6.65 (m, 2H), 6.12 (s, H-3), 4.03 (s, 2H, H-αα'), 3.57 and 3.40 (2s, 6H, NMe_2).

14) For the {3.3} sigmatropic rearrangement of allyl dithiocarbamates, see T. Hayashi, I. Hori and T. Oishi, J.Am.Chem.Soc., 105, 2909 (1983) and references cited therein.

15) For example, the hemiacetal 3a underwent a Wittig reaction with methyl (triphenylphosphoranylidene) acetate to give a C-3 alkylated compound 3 (G = CH_2COOMe) :
^{1}H NMR : δ 6.93 (m, 4H), 5.01 (dd, $J_{3,A}$ 7.9 Hz, $J_{3,B}$ 5.8 Hz, H-3), 4.77 (d, $J_{\alpha,\alpha'}$ 2.3 Hz, H-α), 4.42 (d, H-α'), 3.74 (s, 3H, COOMe), 2.88 (dd, J_{AB} 15.5 Hz, H-A), 2.79 (dd, H-B).

16) Compound 2f was identical with an authentic sample prepared by reduction of the corresponding piperidide according to reference 3.
^{1}H NMR : δ 6.80 (m, 2H), 6.74 (m, 1H) and 6.62 (m, 1H), 5.85 (s, H-3), 2.87 (s, 2H, H-αα'), 2.45 (m, 4H), 1.61 (m, 2H) and 1.44 (m, 2H).

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