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A Simple Synthesis of N-Acetyl-1,4-dihydropyrano[3,4-b]indol-3-one: Evidence for a Stepwise Ionic Pathway in the Generation of Indole-2,3-quinodimethanes.

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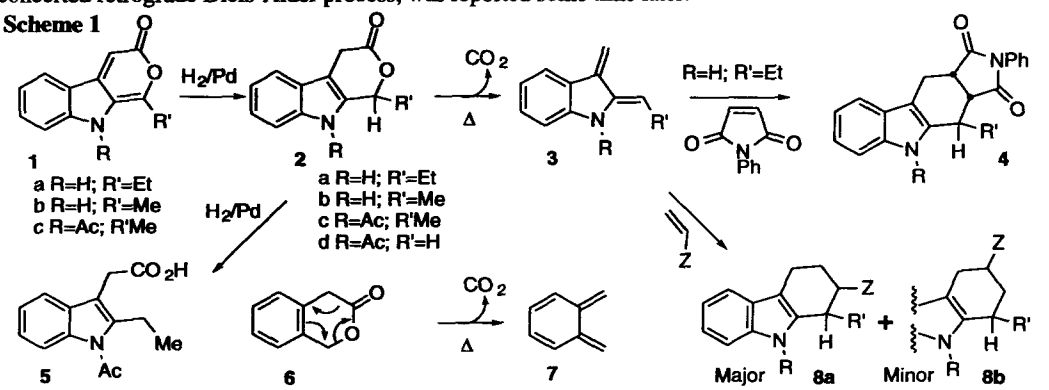
Abstract: The fact that N-acetyl-1,4-dihydropyrano[3,4-b]indol-3-one, prepared from ethyl 2-methylindole-3-acetate in four steps, is inert towards thermal decarboxylation and that decarboxylation of other 1,4-dihydropyrano[3,4-b]indol-3-ones is accelerated by polar solvent and by electron-donating groups suggests that the decarboxylation is an ionic process. © 1997 Elsevier Science Ltd.

Although the synthetic potential of 2,3-dimethylene-2,3-dihydro-1*H*-indoles, so-called indole-2,3-quinodimethanes, **3** has been demonstrated relatively recently in several elegant syntheses of indole natural products, initially by Magnus and co-workers[1] and later by others,[2] the first report of the generation and Diels-Alder trapping of such reactive dienes was that of Pleininger some three decades ago.[3] Catalytic hydrogenation of the pyrano[3,4-b]indole **1** was reported to yield the dihydro-derivative **2a** which, upon thermolysis in the presence of N-phenylmaleimide, yielded an adduct with an elemental composition consistent with that of the Diels-Alder product **4**. The analogous decarboxylation of the isochromanone **6**, under vacuum pyrolysis conditions at 500-600° C, to yield the transient *o*-quinodimethane **7**, believed to be a concerted retrograde Diels-Alder process, was reported some time later.[4,5]

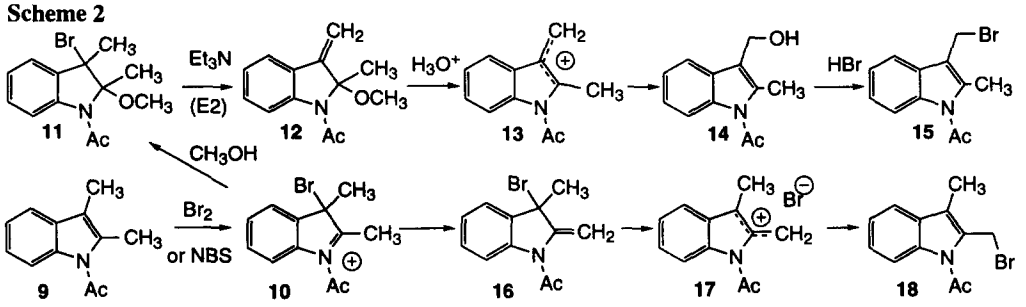
Scheme 1



We have reported the preparation of **2b** using methodology similar to that of Pleininger and have described its thermal decarboxylation and that of its N-acetyl derivative **2c** in the presence of Diels-Alder dienophiles.[6] The regioselectivity of the cycloaddition process with unsymetrical dienophiles was found to be substantially higher in the case of the N-acetyl derivative. Unfortunately, the preparation of **2c** has been found to be problematic. Direct N-acetylation of **2b** was found to proceed in low yield. Although N-acetylation of the corresponding pyrano[3,4-b]indole **1b** proceeded well, subsequent hydrogention was very sluggish and was accompanied by substantial hydrogenolysis at the C-2α-carbon of the indole system which produced the indole-3-acetic acid derivative **5** as a major byproduct. As a result, alternative synthetic strategies towards N-acyldihydropyranoindoles are desirable. We report herein a simple approach to the N-acetyl derivative **2d** of the parent 3,4-dihydropyrano[3,4-b]indole and observations concerning the reactivity of **2d** in thermal decarboxylations which suggest that the decarboxylation process may be a heterolytic reaction.

Our approach to **2d** is based on our previous observations concerning selective side chain functionalization of N-acyl-2,3-dialkylindoles. [7,8] In particular we have shown that selective bromination at the C-2α-carbon atom can be effected with NBS or molecular bromine likely via the mechanism shown below (Scheme 2). On the other hand, selective functionalization at the C-3α-carbon is possible if the bromination intermediate **10** is intercepted at low temperature by addition of methanol followed by elimination of HBr through the use of triethyl amine as base.

Scheme 2

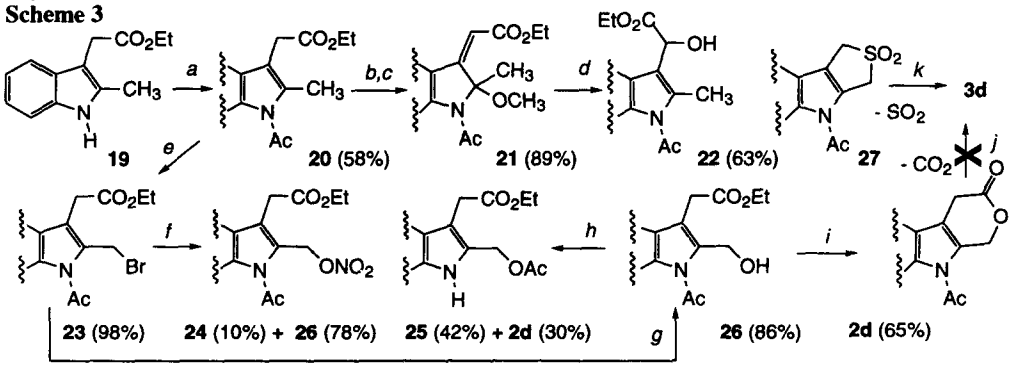


We reasoned that application of this methodology to the N-acetyl derivative **20** of the known indole **19**, derived from levulinic acid via a Fischer indolization,[9] might offer a route to **2d** via **23** and **26** if the presence of the carboalkoxy group in **20** did not perturb the reactivity of this system seriously relative to that of N-acetyl-2,3-dimethylindole (**9**). In practice we have discovered that **20** is readily prepared from **19** by reaction with acetic anhydride with catalysis by *p*-TSA and that the 2-methoxy-3-alkylidene indoline **21** is formed smoothly by low temperature bromination-methanolysis of **20** followed by triethyl amine-induced elimination as described above for **9**. Exposure of **21** to aqueous acid effected overall hydroxylation at the C-3α-carbon atom to give **22**.

Similarly the strategy employed previously to achieve C-2α carbon substitution of **9** was found to be effective with **20**. Thus, reaction of **20** with NBS in refluxing CCl_4 gave the bromide **23** in 98% yield. Exposure of **23** to aqueous THF gave the alcohol **26** but only in low yield (45%). Hydrolysis in the presence of silver nitrate improved the yield of **26** to 78% with the nitrate **24** being formed as a minor contaminant (10%). In larger scale reactions, in which the rate of dropwise addition of silver nitrate solution to the bromide **23** could be controlled more readily, the desired alcohol was obtained cleanly in 86% yield. It was recognized

from the outset that the alcohol **26** might undergo two types of acyl transfer reactions. Precisely what reaction conditions would favour the desired nucleophilic attack by the hydroxyl group on the ethyl ester to yield the lactone **2d** over the undesirable nucleophilic attack on the N-acetyl group which would result in N-O acyl transfer to yield the acetate **25** was not known. After some experimentation, it was found that formation of the acetate **25** was favoured in a 1:1 mixture of THF and pH 7 phosphate buffer, whereas formation of the lactone **2d** was favoured in refluxing benzene solution in the presence of a catalytic amount of *p*-TSA as the acid catalyst. Thus, the lactone **2d** was obtained in four steps in 32% overall yield from the known indole **19.**

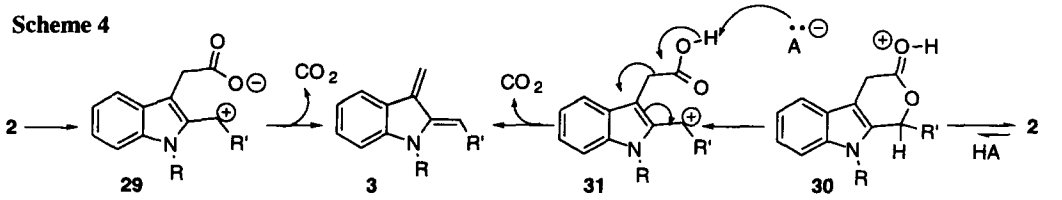
Scheme 3



(a) Ac_2O/*p*-TSA ; (b) Br_2/MeOH/40°; (c) Et_3N; (d) H_2O/CH_3CN/*p*-TSA/reflux; (e) NBS/CCl_4; (f) $AgNO_3/H_2O$; (g) $AgNO_3/H_2O$/slow addition; (h) pH 7; (i) *p*-TSA/Ph-H/reflux ; (j) DMF/reflux; (k) benzene/reflux

With **2d** available by this method and samples of **2b** and **2c** available from previous work, we turned our attention to a study of the influence of N_1 and C-2α substitution on the thermal decarboxylation of these indole-2,3-quinodimethane precursors. We have discovered that whereas **2b** undergoes rapid decarboxylation under relatively mild conditions (< 1 h at 115°), the N-acetyl analogue **2c** reacts more slowly (~ 5 h at 125°) . Furthermore we have found that **2d** is essentially inert with respect to decarboxylation even in refluxing DMF overnight. Furthermore, **2c** is much less reactive with respect to decarboxylation when chlorobenzene is employed in place of DMF (~ 94 h at 140° for complete reaction). This lack of reactivity of **2d** with respect to expulsion of CO_2 to generate the indole-2,3-quinodimethane system contrasts dramatically with the ease of extrusion of SO_2 from the dihydrothienoindole dioxide **27** (Scheme 3) in reluxing benzene observed previously in this laboratory.[6] These effects of solvent and of structure on the rate of decarboxylation prompted us to consider poetential implications with respect to the nature of the reaction mechanism of the decarboxylation process which has received little attention in the literature.

Scheme 4



In particular, we feel that the diminution of the rate of decarboxylation upon introduction of an electron-withdrawing N-acetyl group is consistent with the formation of a zwitterionic intermediate such as **28** as is the rate-accelerating effect of introduction of a C-2α-alkyl substituent. In addition, the observation of rate acceleration of the decarboxylation in a dipolar solvent is most readily rationalized on the basis of a mechanism such as that shown in Scheme 4. The conclusion that this process involves a heterolytic cleavage reaction prompted us to consider the possibility that, for the inert system **2d**, decarboxylation might be achieved through the use of an acid catalyst. In practice we have found that addition of a weak acid such as acetic acid to a sample of **2d** subjected to the decarboxylation conditions in refluxing chlorobenzene containing methyl acrylate does result in the formation of the known mixture of adducts **8** (R = Ac; R' = H; Z = CO_2Me) albeit in very low yield (3% isolated yield along with recovered starting material 56%) suggesting that further explorations of acid catalysis of the decarboxylation process are in order.

Extensions of this synthetic approach to N-acyldihydropyranoindoles to variously substitued analogues and studies of the influence of substituents at the C-2α and C-3α positions on the rate of decarboxylation and the regioselectivity of the Diels-Alder reactions of the corresponding indole-2,3-quinodimethanes are in progress.

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References and Notes:

1. (a) Gallagher, T.; Magnus, P. *Tetrahedron*, **1981**, 3889. (b) Magnus, P.D.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (c) Magnus, P. in *Strategies and Tactics in Organic Synthesis*, **1984**, Lindberg, T. (Ed.), Academic Press, Inc., Orlando. (d) Magnus, P.; Sear, N.L. *Tetrahedron* **1984**, *40*, 2795. (e) Magnus, P.D.; Pappalardo, P.A. *J. Am. Chem. Soc.* **1986**, *108*, 212.(f) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242. (g) Magnus, P.; Katoh, T.; Matthews, I.R.; Huffman, J.C. *J. Am. Chem. Soc.* **1989**, *111*, 6707.
2. For a review of the chemistry of indole-2,3-quinodimethanes see: Pindur, U.; Erfanian-Abdoust, H. *Chem. Rev.* **1989**, *89*, 1681. For examples of so-called stable indolequinodimethane analogs see: (a)pyrano[3,4-b]indoles: Moody, C.J.; May, C. *J. Chem. Soc. Perkin Trans. I* **1988**, 247; Pindur, U.; Erfanian-Abdoust, H. *Liebigs Ann. Chem* **1989**, 227. (b) furano[3,4-b]indoles: Gribble, G.; Saulnier, M.G. *Tetrahedron Lett.* **1983**, *24*, 5435. (c) pyrollo[3,4-b]indoles: Sha, C.-K.; Chuang, K.-S.; Wey, S.-J. *J. Chem. Soc. Perkin Trans. I* **1987**, 977.
3. Pleininger, H.; Muller, W.; Weinerth, K. *Chem. Ber.* **1964**, *97*, 667.
4. Spangler, R.J.; Beckman, B.G.; Kim, J.H. *J. Org. Chem.* **1977**, *42*, 2989.
5. For reviews of *o*-quinodimethane chemistry see: (a) Charlton, J.L.; Alauddin, M.M. *Tetrahedron* **1987**, *43*, 2873. (b) Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proc. Int.* **1991**, *23*, 237.
6. Dmitrienko, G.I.; Vice, S.F.; Nandin de Carvalho, H.; Taylor, N.J. *Tetrahedron Lett.* **1989**, *30*, 7289.
7. Vice, S.F.; Dmitrienko, G.I. *Can. J. Chem.* **1982**, *60*, 1233.
8. Dmitrienko, G.I.; Vice, S.F.; Copeland, C.R.; Forsey, S.P. *Tetrahedron Lett.*, **1985**, *26*, 5253.
9. Bullock, M.W.; Fox, S.W. *J. Am. Chem. Soc.* **1951**, *73*, 5155.

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