Tetrahedron Letters, Vol.22, No.30, pp 2843 - 2846, 1981
Printed in Great Britain

0040-4039/81/302843-04$02.00/0

1,2,3,4-TETRASUBSTITUTED ISOQUINOLINE ACETIC ACIDS

by Rodney C. Schnur* and Harry R. Howard

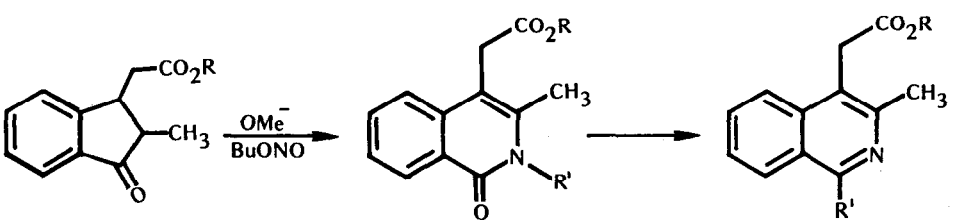
(Central Research, Pfizer Inc., Groton, CT 06340)

Differentially tetrasubstituted isoquinolines are now conveniently prepared by rearrangement of the readily obtainable indanones.

A versatile synthesis of 3-alkyl-4-isoquinoline acetic acids[1] variously substituted in the 2-position and/or the 1-position has been developed based upon the 1-indanone to 2-hydroxyisocarbostyril rearrangement.[2] While substituent effects at the 2-position of 1-indanone have been reported,[3] the rearrangement of 2,3-disubstituted 1-indanones has not been investigated. This approach provides for the efficient preparation of a variety of 3,4-dialkyl isoquinolines which can be subsequently elaborated at the more reactive 1- and 2-positions thus resulting in a good general synthesis of 1,2,3,4-tetrasubstituted isoquinolines with the practical advantages of a short reaction sequence overall and inexpensive starting materials.

Although entry into such tetra functionalized isoquinolines via the readily available homophthalimide is conceivable, two deficiencies of this approach are encountered. The first results from the difficulty in preparing selectively the requisite 4-monosubstituted homophthalimides.[4,5] The second lies in the difficulty in elaborating the less reactive 3-position of isoquinolines late in a synthetic sequence when all the other desired functionality has been secured[5]. Thus, early establishment of 3-position functionality was sought.

Scheme I



1a R = H
1b R = CH_3

2a R = H; R′ = OH
2b R = CH_3; R′ = OH
2c R = R′ = H
2d R = CH_3; R′ = 3,4—$OCH_2C_6H_3Cl_2$
2e R = H; R′ = 3,4—$OCH_2C_6H_3Cl_2$
2f R = H; R′ = 3,4—$CH_2C_6H_3Cl_2$

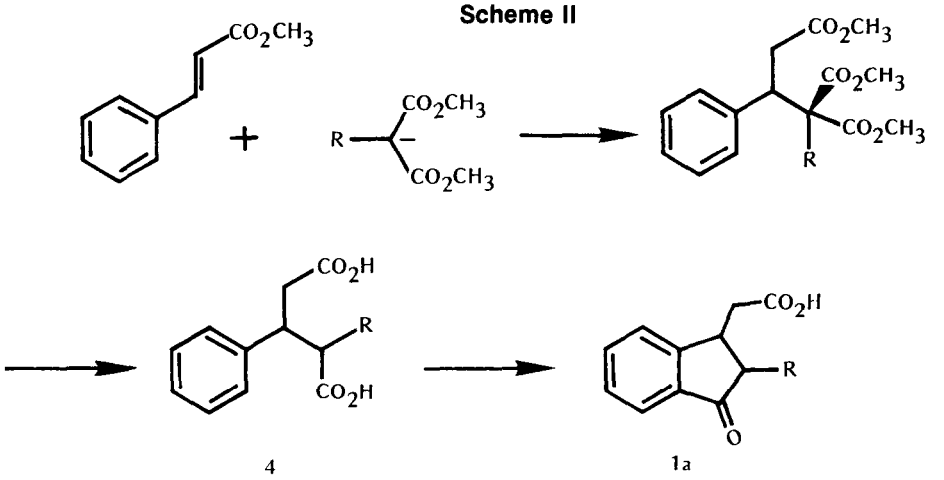
3a R = H; R′ = Cl
3b R = H; R′ = 4—OC_6H_4Cl
3c R = H; R′ = 4—$NH(CH_3)CH_2C_6H_4Cl$
3d R = H; R′ = 3,4—$OCH_2C_6H_3Cl_2$

The key reaction in this synthesis (Scheme I) is the transformation of 2-methyl-1-oxo-indan-3-acetic acid[6], **1a**, to 2-hydroxy-3-methyl-isocarbostyril-4-acetic acid, **2a**[7], mp 198-200 °C (67%), after treatment with K^+OtBu^- and BuONO in methanol at 20 °C by way of an oximino-ester acid. Ester **2b**, mp 185-190 °C, was less efficiently prepared (42%) analogously from **1b** (prepared from **1a** by treatment with diazomethane). Reduction of N-hydroxy compound **2a** to amide **2c**, mp 295 °C dec, (89%) was accomplished by heating with one equiv of PCl_3 in ethyl

acetate at 80 °C for 1 5 h [8] Alkylation of either **2b** or **2c** with 3,4-dichlorobenzyl chloride afforded the expected products, **2d**, mp 90-94 °C, or **2f**, mp 218-220 °C, respectively Saponification of **2d** with 1 equiv NaOH in 5 1 dioxane water gave **2e** mp 222 °C dec (45%) Alternatively **2a** was transformed to the isoquinoline **3a**, mp 121-3 °C dec (92%) by reaction with $PCl_3/POCl_3$ at 100 °C for 20 hr Subsequent replacement of the chlorine with phenoxide, amine, or alkoxide using traditional methods gave **3b**, mp 192-5 °C, **3c**, oil, or **3d**, mp 180-3 °C respectively

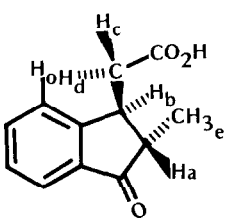
The versatility of this isoquinoline synthesis is dependent upon the availability of polysubstituted indanones These key intermediates may be prepared by a number of methods including, for example, ones initiating from variously substituted cinnamates Acid **1a** was obtained by the method of Molho, Scheme II, who reported one product, **1a**, from the cylization of unsymmetrical glutaric acid, **4**

Scheme II

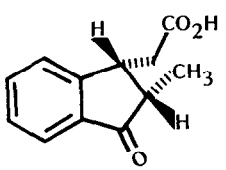


4 1a

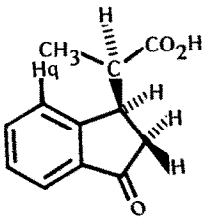
However, four pairs of diastereomers can arise from this cyclization involving either of the two carboxylates leading to a *trans* (**5**) and *cis* (**6**) 2-methyl-1-oxo-indan-3-acetic acid and a *threo* and *erythro* (**7** and **8** respectively) α-methyl-1-oxo-indan-3-acetic acid, along with their mirror images



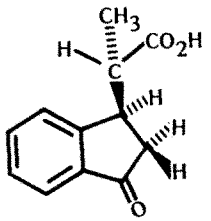
5



6



7



8

A 270 mHz NMR spectrum of the reaction mixture, obtained using his procedure, prior to product crystallization clearly shows the presence of the expected four distinct methyl doublets in the ratio 75:9:12:4 at chemical shifts 1.370 δ, 1.249 δ, 1.215 δ, and 0.944 δ[9] respectively with the major component being assigned structure **5**, the *trans* isomer, based on coupling constants.[6,10] The regioselectivity for the observed mode of cyclization may derive from the relative differences in steric interactions between the *ortho* proton, H_o, on the benzene ring and the methylene hydrogens *alpha* to the carboxylate, **5**, versus those same *ortho* proton, H_q, interactions with the methyl group *alpha* to the other carboxylate, **7**.

The reaction of the diastereomeric indanone mixture with alkoxide and alkyl nitrite afforded only isoquinoline **2a**. No 3-unsubstituted isoquinoline derived from **7** and/or **8** was obtained.[11] Thus a variety of 1,2,3,4-tetrasubstituted isoquinolines are readily prepared by Scheme II requiring only the appropriately substituted 3-phenyl propionic acids as ultimate precursors.[12]

We thank Dr. E. Whipple for NMR studies on the diastereomeric indanones.

FOOTNOTES

1. These compounds are aldose reductase inhibitors potentially useful in treatment of diabetic complications; R.C. Schnur, manuscript in preparation. For reviews on isoquinolines syntheses see: W.J. Gensler, "Isoquinolines" in Heterocyclic Compounds, Vol. 4, R.C. Elderfield Ed., J. Wiley and Sons. NY 1952 pp 344-490: R.H. Manske, Chem. Rev. **30,** 145 (1942): M.H. Palmer, "The Structure and Reactions of Heterocyclic Compounds," Edward Arnold Publishers Ltd., London pp 145-165 1967: and N.V. Sidgwick, "The Organic Chemistry of Nitrogen." Clarendon Press, Oxford 1966 pp 730-736.

2. E.J. Moriconi, F.J. Creegan, C.K. Donovan, and F.A. Spano, J. Org. Chem., **28,** 2215 (1963).

3. E.J. Moriconi and F.J. Creegan, J. Org. Chem., **31,** 2090 (1966).

4. G.N. Walker, J. Org. Chem., **37,** 3955 (1972).

5. The predominant alkylation products of homophthalimide are 4,4 disubstituted; D. Ben Ishai, Z. Inbal, and A. Warshawsky, J. Het. Chem., **7,** 615 (1970): C. Fournier, C.R. Acad. Sci. Paris Ser. C, **268,** 846 (1969); see also G. Jones, J. Chem. Soc., **1960,** 1896; T. Kametani, K. Kigasawa and M. Huragi. Chem. Pharm. Bull., **15,** 704 (1967); F-H. Marquardt, Helv. Chem. Acta, **50,** 1477 (1967); M.M. Robinson, J. Am. Chem. Soc., **80,** 5481 (1958); A.F.A. Shalaby, A.A. El-Sazed and H.A. Daboun, J. Prakt. Chem., **313,** 1039 (1971).

6. D. Molho and M. Giraud, Bull. Soc. Chim. Fr., **1970,** 1143.

7. Satisfactory spectral and analytical data (except **3c**) were obtained on all new compounds.

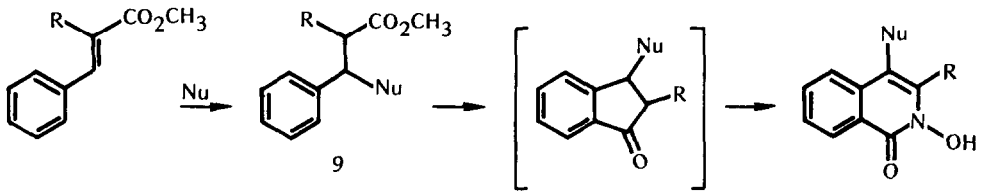
8 Moriconi reports the reduction of N-hydroxy-3-methyl isocarbostyril with iodine/red phosphorous in glacial acetic acid at reflux for 14 hr in 32% yield [2]

9 $J_{CH_3—CH}$ = 7 43, 7.65, 7 18, and 7 14 Hz respectively

10 The coupling constants of **7** were measured as $J_{CH_3,a}$ = 7 43 Hz, J_{a-b} = 3 9 Hz, J_{b-c} = 8 5 Hz, J_{b-d} = 5 6 Hz, and J_{c-d} = 16 2 Hz The chemical shifts were H_a = 2.500 δ, H_b = 3 3978 δ, H_c = 2 695 δ, and H_d = 2 965 δ

11 2-Unsubstituted indanones yield 1,2-indandione-2-oximes under these conditions.[2] Simchen has obtained 1,3 dichloro isoquinolines from the rearrangement of 1,2-indanedione-2-oximes with PCl_5, G Simchen and W Kramer, Ber , **102**, 3666 (1969).

12 While the C-1 carbons of **5** and **6** derive from malonate, the C-1 carbons of **7** and **8** derive from the original cinnamate carbonyl in Scheme II and the nucleophile malonate eventually occupies the 3-position of indanone Thus, the scope of this approach is not restricted to using malonates as nucleophiles and a wide variety of 2,3-disubstituted-3 phenyl propionates, **9**, possibly originating from cinnamates can be envisioned as suitable starting materials for the preparation of 1,2,3,4 substituted isoquinolines



(Received in USA 20 April 19)