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THE TOTAL SYNTHESIS OF ±-ISORETRONECANOL FROM PYRROLE+

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Summary: A total synthesis of ±-isoretronecanol from pyrrole is described which uses several novel pyrrole reactions including an intramolecular nucleophilic displacement reaction on a toluenesulfonyl-activated pyrrole followed by reductive removal of the activating group.

Previous work from our laboratory has described the sulfinylation of pyrroles in the 2-position[1], the acid catalyzed isomerization of the resulting pyrrol-2-yl sulfoxides to the corresponding 3-isomers[1], the additive Pummerer chlorination of pyrrol-3-yl sulfloxides[2], the addition of pyrrol-1-yl anions to activated cyclopropanes to give 2-(pyrrol-1-yl)ethyl-malonates[3] and the cyclization of such malonates onto appropriately activated pyrrole rings[3]. In this communication we report the use of these five novel reactions in a sequence which leads to the total synthesis of ±-isoretronecanol from pyrrole. Noteworthy in this synthesis is the use of the toluenesulfonyl substituent to activate a pyrrole ring to nucleophilic attack, followed by reductive removal of this activating group.

Thus, pyrrole was reacted with toluenesulfinyl chloride[4] in methylene chloride to afford a mixture of the 2- and 3-toluenesulfinyl pyrroles (1) and (2) which was converted entirely to (2) by treatment with trifluoroacetic acid at 0°C[1]. The sulfoxide (2) obtained in 45% yield was treated at -75°C with oxalyl chloride in the presence of sodium bicarbonate suspended in methylene chloride, and then oxidized with excess m-chloroperbenzoic acid to give 2-chloro-3-toluenesulfonylpyrrole (3) in 61% yield[2].

The anion of (3), formed with sodium hydride in dimethylformamide at 25°C, was treated with spiro[2.5]5,7-dioxa-6,6-dimethyloctan-4,8-dione[5] at 60°C. Transesterification of the crude adduct thus formed with methanolic hydrogen chloride gave dimethyl 2-(2-chloro-3-p-toluenesulfonylpyrrol-1-yl)ethylmalonate (4) in 90% yield[7]. Formation of the corresponding malonate anion with sodium hydride in DMF followed by heating at reflux under argon gave an approximately 1:1 mixture of cyclized esters (5a) and (5b) in about 73% yield. While separation of the product mixture was difficult, this was not necessary, since basic hydrolysis and decarboxylation gave a single acid (5c)[8] in 63% overall yield from (4). Reesterification with diazomethane gave monoester (5b)[9] in 98% yield.

Treatment of 5b with excess lithium aluminum hydride in refluxing dioxane gave 1-hydroxymethyl-1,2-dihydro-3H-pyrrolo[1.2.a]pyrrole (6) in 32% yield[10], identical to the compound obtained in 94% yield by the basic hydrolysis and LAH reduction of the known[6] 1-cyano-1,2-dihydro-3H-pyrrolo[1.2.a]pyrrole (7). Finally, hydrogenation of (6) with rhodium on alumina at one atmosphere gave ±-isoretronecanol (8), identified as the picrate, mp 188-189°C, (lit. mp 189.5-190°C)[11].

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References and Notes

1. O. Carmona, R. Greenhouse, R. Landeros, J.M. Muchowski, J. Org. Chem., 45, 5336 (1980).
2. J. Garcia, C. Ortiz, R. Greenhouse, submitted for publication.
3. F. Franco, R. Greenhouse, J.M. Muchowski, J. Org. Chem., 47, 1682 (1982).
4. Organic Synthesis, coll. vol. IV, 937 (1963).
5. R.K. Singh, S. Danishefsky, J. Org. Chem., 40, 2969 (1975).
6. H. Carpio, E. Galeazzi, R. Greenhouse et al., Can. J. Chem., 60, 2295 (1982).
7. mp 85-87°C; IR: 1760, 1745, 1315, 1140 cm^{-1}; NMR (300 mHz): 7.86 (d,2H), 7.29 (d,2H), 6.64 (d,1H,J=3.3), 6.62 (d,1H,J=3.3), 3.97 (t,2H), 3.72 (s,6H), 3.32 (t,1H), 2.40 (s,3H), 2.30 (m,2H); MS: 413, 415 (M+.); Calcd. for $C_{18}H_{20}ClNO_6S$ (413.89): C, 52.24; H, 4.87; N, 3.38; Found: C, 52.21; H, 4.93, N. 3.39.
8. mp 197-198°C; IR: 3465, 1735, 1280, 1120 cm^{-1}; NMR: 7.75 (d,2H), 7.31 (d,2H), 6.84 (d,1H, J=2.9), 6.37 (d,1H,J=2.9), 4.06 (dd,1H,J=9.2,3.7), 4.00 (m,2H), 2.86 (m,1H), 2.54 (m,1H), 2.34 (s,3H); MS. 306 (M+.); Calcd. for $C_{15}H_{15}NO_4S$ (305.36): C, 59.00; H, 4.95; N, 4.59; S, 10.50; Found: C, 58.78; H, 4.97; N, 4.56; S, 10.65.
9. mp 131-132°C; IR: 1745, 1294, 1122 cm^{-1}; NMR: 7.79 (d,2H), 7.26 (d,2H), 6.63 (d,1H, J=2.9) 6.50 (d,1H,J=2.9), 4.28 (m,1H), 4.13 (m,1H), 3.98 (m,1H), 3.67 (s,3H), 2.82 (m,1H), 2.69 (m,1H), 2.38 (s,3H); MS: 319 (M+.); Calcd. for $C_{16}H_{17}NO_4S$ (319.38): C, 60.17; H, 5.37; N, 4.39; S, 10.04; Found: C, 60.21; H, 5.45; N, 4.28; S. 10.13.
10. oil, IR: 3407 cm^{-1}; NMR: 6.62 (dd,1H,J=1.22, 2.54), 6.24 (t,1H,J=2.54), 5.88 (m,1H), 3.98 (m,2H), 3.72 (m,2H), 3.33 (m,1H), 2.67 (m,1H), 2.36 (m,1H); MS: 137 (M+.); HRMS: calcd. for $C_8H_{11}NO$: 137.0841; Found: 137.0842.
11. N.J. Leonard, T. Sato, J. Org. Chem., 34, 1066 (1969).

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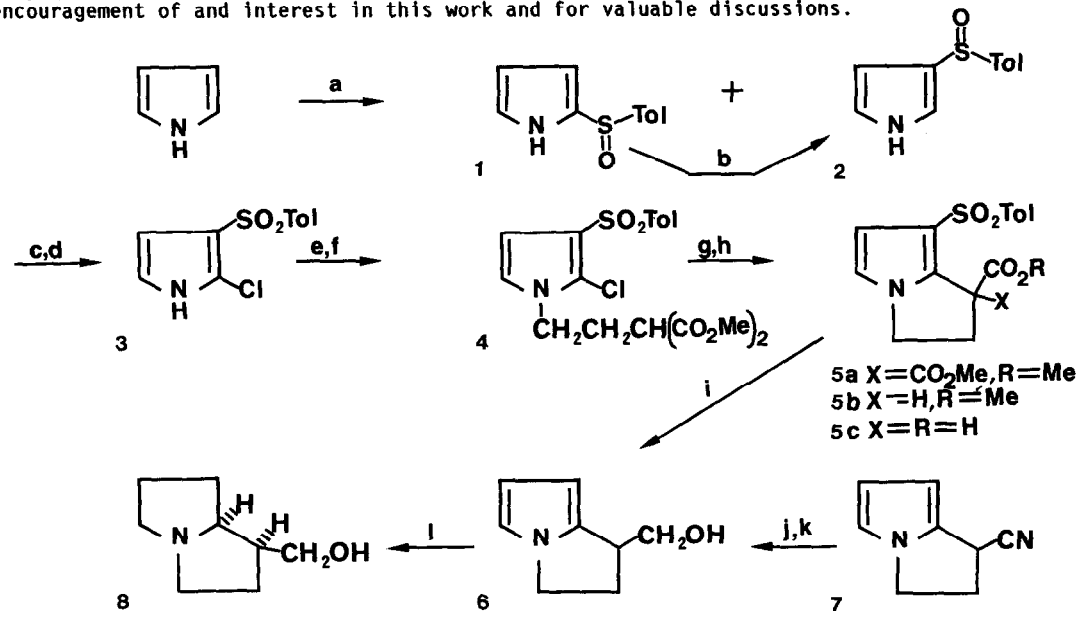

a. Toluenesulfinyl chloride, CH_2Cl_2, 0°C; b. CF_3CO_2H, CH_2Cl_2, 0°C; c. Oxalyl chloride, CH_2Cl_2, $NaHCO_3$, -78°C; d. m-chloroperbenzoic acid, CH_2Cl_2, 0°C; e. NaH, DMF; spiro[2.5]5,7-dioxa-6,6-dimethyloctan-4,8-dione; f. MeOH, HCl, 0°C; g. NaH, DMF, reflux; h. NaOH, H_2O, MeOH; CH_2N_2, CH_2Cl_2; i. LAH, dioxane, reflux; j. KOH, ethanol, H_2O; k. LAH, THF, 25°C; l. Rh/Al_2O_3 H_2 1 atm.

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