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CANNABIS XXIV. A NEW CONVENIENT SYNTHESIS OF CANNABINOL

J. Novák and C.A. Salemink

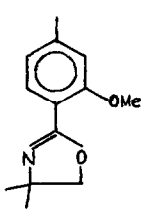
Laboratory of Organic Chemistry, State University,
Utrecht, The Netherlands

Summary: The key step in a new synthetic approach to cannabinol 5 is a remarkably smooth methoxy displacement in the o-methoxyaryloxazoline 1 affording sterically hindered biaryloxazoline 3.

We wish to report some important results from our studies concerning the total synthesis of cannabinoids[1] leading to a new, high yield synthesis of cannabinol. Cannabinol is a minor constituent of Cannabis sativa L. and is considered as an oxidative degradation product of the psychoactive principle, Δ^1-tetrahydrocannabinol.

To synthesize a biphenylic precursor of cannabinol we chose the oxazoline facilitated methoxy substitution in o-methoxyaryloxazolines by organometallics recently discovered by Meyers et al.[2]. Applying their general reaction conditions (THF, 20°) to the Grignard reagent 2[3] and oxazoline 1[4] however, resulted in a very low conversion, only 4%. To our surprise, we could dramatically improve the yield of this key step to 87% performing the reaction simply by refluxing in tetrahydrofuran. This modification seems to lower largely the steric requirements of the methoxy displacement and is so far the most preferable route to sterically hindered unsymmetrical biphenyls.

A typical procedure was as follows. The Grignard reagent (2 equiv.)[5] from 14,5 g of 2-bromo-1,3-dimethoxy-5-pentylbenzene[3] and 1,5 g of magnesium in THF (35 ml) was added to a solution of 1[4] (5,5 g) in THF (45 ml). The mixture was stirred and refluxed for 22 hrs, cooled, diluted with water and extracted with ether. Work-up yielded an oil, from which any by-products were distilled off up to 150° (0,12 mm). The distillation residue was a very viscous oil, 8,6 g/87%/, pure according to ^{1}H NMR analysis[7].



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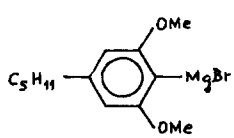

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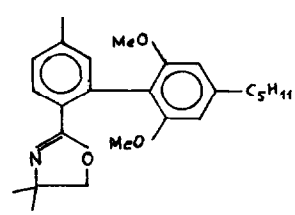

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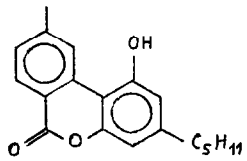

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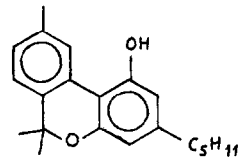

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The hydrolysis of the oxazoline moiety in 3, followed by cleavage of both methoxy groups and acid catalyzed cyclization to the lactone 4 was performed in a new manner and with a very high yield as a "one-pot" reaction by HI/Ac_2O. Hydrolysis with aq. 4,5 N HCl according to Meyers et al.[2] gave only a mixture of the dimethoxy acid and the methoxy lactone, free of the required hydroxy lactone 4. Thus, 57% aq. HI (5 ml) was added dropwise under cooling to 20° to a solution of 3 (0,50 g) in Ac_2O (5 ml). The mixture was stirred and refluxed for 2 hrs, cooled, diluted with water and extracted with EtOAc. Work-up yielded 0,37 g (99%) of yellow crystals, m.p. 181°. A sample was further purified by crystallization (MeOH) affording analytically pure material, m.p. 185° [8].

The final step, the conversion of lactone 4 to cannabinol 5 by MeMgI followed by acidification, was already described by Adams et al.[8] in 75% yield.

Comparing our cannabinol synthesis with the known syntheses[9], the difficult aromatization of the terpenoid part is now omitted and the substitution in the olivetol moiety is fully regiospecific.

References and notes

1. J. Novák and C.A. Salemink, Tetrahedron Lett. 1981, 1063.
2. A.I. Meyers, R. Gabel and E.D. Mihelich, J. Org. Chem. 1978, 43, 1372.
3. 2-Bromo-1,3-dimethoxy-5-pentylbenzene, b.p. 115-120°/0,12 mm, was prepared as a new compound in 75% yield from 1,3-dimethoxy-5-pentylbenzene by lithiation (BuLi, hexane, ether), followed by treatment with 1,2-dibromethane under ethylene evolution. ^{1}H NMR (CCl_4) of 2-bromo-1,3-dimethoxy-5-pentylbenzene: δ 0,9 (3H,t), 1,2-1,75 (6H,m), 2,5 (2H,t), 3,8 (6H,s), 6,3 (2H,s). For analogy see J.R. Cannon et al., J. Chem. Soc., C, 1971, 3495.
4. The new oxazoline 1, m.p. 54-55° (cyclohexane), was synthesized from the corresponding acid[6] by the procedure of Meyers et al.[2] in 76% overall yield.
5. Working at 1:1 molar ratio[2] leads to yields around 65% only.
6. J.E. Davies and J.C. Roberts, J. Chem. Soc. 1956, 2173.
7. ^{1}H NMR ($CDCl_3$) of 3: δ 0,9 (3H,t), 1,2 (6H,s), 1,2-1,8 (6H,m), 2,35 (3H,s), 2,6 (2H,t), 3,7 (8H,s), 6,4 (2H,s), 7,1 (1H,s), 7,15 (1H,d,further splitted), 7,75 (1H,d).
8. R. Adams, B.R. Baker and R.B. Wearn, J. Am. Chem. Soc. 1940, 62, 2204.
9. R.K. Razdan in J. ApSimon, Ed., The Total Synthesis of Natural Products, Vol. 4, Wiley-Interscience, New York, 1981.

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