A New and Efficient Synthesis of 5-Alkylresorcinol Dimethyl Ethers

J. NOVÁK, C. A. SALEMINK

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

In connection with synthetic work on cannabinoids[1,2], large quantities of the key intermediate, olivetol dimethyl ether (5-pentyl-1,3-dimethoxybenzene), were required. Several two-step syntheses of olivetol dimethyl ether have been reported[3-7] but we found none of these satisfying due to either inconvenience when working on a larger scale[3,4,5] or the use of expensive starting materials[6,7].

We now report a convenient, one-step synthesis of olivetol dimethyl ether (**4**; $R = C_5H_{11}$) from commercially available 5-chloro-1,3-dimethoxybenzene (**1**) and 1-iodopentane (**3**; $R = C_5H_{11}$) via the dilithium tetrachlorocuprate-catalyzed Grignard cross-coupling[8]. The coupling is effected by adding a mixture of 1-iodopentane and a catalytic amount of dilithium tetrachlorocuprate dissolved in tetrahydrofuran to a cooled, stirred solution of the Grignard reagent from 5-chloro-1,3-dimethoxybenzene (**1**) in tetrahydrofuran. In contrast to the known dilithium tetrachlorocuprate-catalysis of the coupling of alkylmagnesium halides with alkyl halides the coupling of arylmagnesium halides under these conditions is practically unknown. We could only find one example[9] of the use of an arylmagnesium halide. When the reaction was first investigated by us, with 1-bromopentane using standard conditions[8], the yield was low (22%). In the following detailed study, including over thirty experiments, the yield could be step-wise increased to 66% by using more catalyst, substituting 1-iodopentane for 1-bromopentane, and reducing the amount of solvent. Increasing the amount of 1-iodopentane did not affect the yield significantly. On the other hand, no positive effect was achieved by increasing the reaction temperature nor lengthening the reaction time. Substituting pentyl tosylate[10] for 1-iodopentane resulted in a somewhat lower yield. Decreased yields were noted on adding various co-solvents like benzene, hexamethylphosphoric triamide, diethyl ether, 1,2-dimethoxyethane, or dioxan. We have also tried other coupling catalysts, however, lower yields were obtained using copper(I) iodide/2,2'-bipyridine[11] or iron(III) chloride[12]. A lower yield (35-40%) was reached in the nickel-phosphine complex-catalyzed reaction of pentylmagnesium bromide with 5-chloro-1,3-dimethoxybenzene applying the general reaction conditions of Tamao et al.[13].

Finally, we tried various other 1-iodoalkanes **3** to test the general applicability of our method. Without exception, the yields of the expected 5-*n*-alkylresorcinol dimethyl ethers **4** were good (Table). The present method is less useful for the synthesis of resorcinol ethers with branched alkyl groups as demonstrated on 5-isopropyl-1,3-dimethoxybenzene (**4f**; $R = i\text{-}C_3H_7$; 16%). Coupled with a demethylative step[3] our method, developed primarily to obtain olivetol dimethyl ether, also compares favourably with the up to now shortest olivetol synthesis[14]. The presented results show that the dilithium tetrachlorocuprate catalyst is more useful than the well-known, but more expensive nickel-phosphine catalysts in the synthesis of arylalkanes via a cross-coupling reaction.

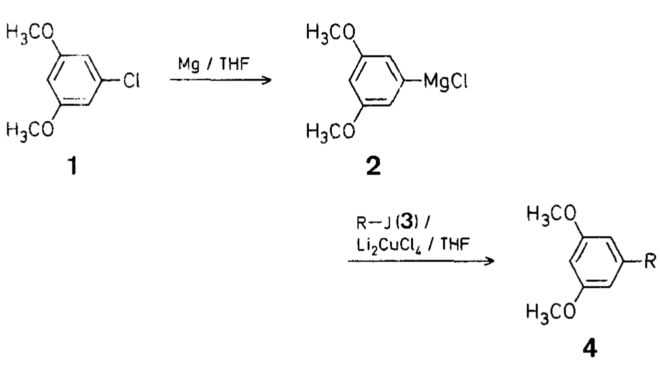

Table. 5-Alkylresorcinol Dimethyl Ethers 4 prepared

Product[a] No.	R	Yield [%]	b.p. [°C]/torr found	b.p. [°C]/torr reported
4a	CH_3	74	105-106°/12	102°/8[15]
4b	C_2H_5	74	117-118°/12	123°/14[16]
4c	$n\text{-}C_4H_7$	72	130-131°/12	136-137°/16[17]
4d	$n\text{-}C_4H_9$	70	141-143°/12	125-128°/6[18]
4e	$n\text{-}C_5H_{11}$	66	152-156°/12	106-110°/2[6]
4f	$i\text{-}C_3H_7$	16	–[b]	

[a] The identity and purity (≥97%) of each product was further confirmed by ^{1}H-N.M.R. spectrometry.

[b] Not isolated.

Olivetol Dimethyl Ether (4e):

The Grignard reagent **2** is prepared from 5-chloro-1,3-dimethoxybenzene (**1**; from Aldrich; 40 g, 0.23 mol) and magnesium (6 g, 0.25 mol) in tetrahydrofuran (80 ml) with a small amount of 1,2-dibromoethane as the starter during a 6 h reflux period under dry nitrogen. To this ice-cooled, stirred solution, a mixture of 1-iodopentane (**3e**; from Merck-Schuchardt; 42.6 ml, 0.325 mol) and the dilithium tetrachlorocuprate catalyst (30 ml of a 0.2 molar solution in tetrahydrofuran) is added dropwise over a period of 30 min. The resulting black mixture is stirred at 0 °C for 90 min and at 20 °C for additional 16 h. The almost solid reaction mixture is acidified with 6 normal hydrochloric acid (160 ml) and extracted with diethyl ether (2 × 200 ml). The organic extract is washed with aqueous 15% ammonia (60 ml) and water (60 ml), dried with magnesium sulfate, and evaporated in vacuo. According to the ^{1}H-N.M.R. spectrum of the residual product olivetol dimethyl ether **(4e)** is formed in 74% yield. Distillation affords the pure product as a colorless liquid; yield: 31.9 g (66%); b.p. 152–156 °C/12 torr (Ref.[6], b.p. 106–110 °C/2 torr). The I.R. and ^{1}H-N.M.R. spectra of the product are identical with the spectra of an authentic sample[4].

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[1] J. Novák, C. A. Salemink, *Tetrahedron Lett.* **23,** 253 (1982).

[2] J. Novák, C. A. Salemink, *Tetrahedron Lett.* **24,** 101 (1983).

[3] P. Baeckström, G. Sundström, *Acta Chem. Scand.* **24,** 716 (1970).

[4] K. Bailey, *Can. J. Chem.* **52,** 2136 (1974).

[5] A. J. Birch, J. Slobbe, *Tetrahedron Lett.* **1976,** 2079.

[6] H. Achenbach, W. Kohl, B. Kunze, *Chem. Ber.* **112,** 1841 (1979).

[7] A. A. Durrani, J. H. P. Tyman, *J. Chem. Soc. Perkin Trans. 1* **1980,** 1658.

[8] M. Tamura, J. Kochi, *Synthesis* **1971,** 303.

[9] L. Friedman, A. Shani, *J. Am. Chem. Soc.* **96,** 7101 (1974).

[10] G. Fouquet, M. Schlosser, *Angew. Chem.* **86,** 50 (1974); *Angew. Chem. Int. Ed. Engl.* **13,** 82 (1974).

[11] J. Tsuji, M. Kaito, T. Takahashi, *Bull. Chem. Soc. Jpn.* **51,** 547 (1978).

[12] G. Vavon, P. Mottez, *C. R. Acad. Sci.* **218,** 557 (1944).

[13] K. Tamao et al., *Bull. Chem. Soc. Jpn.* **49,** 1958 (1976).

[14] J. Gosteli, *German Patent* 2359410 (1974); *C. A.* **81,** 91205 (1974).

[15] H. Walbaum, A. Rosenthal, *Ber. Dtsch. Chem. Ges.* **57,** 770 (1924).

[16] J. P. Brown, N. J. Cartwright, A. Robertson, W. B. Whalley, *J. Chem. Soc.* **1949,** 859.

[17] H. Thoms, *Ber. Dtsch. Chem. Ges.* **36,** 3446 (1903).

[18] C. M. Suter, A. W. Weston, *J. Am. Chem. Soc.* **61,** 232 (1939).