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Unexpected Aldol Condensations Under Williamson Arylmethyl Ether Synthesis Conditions

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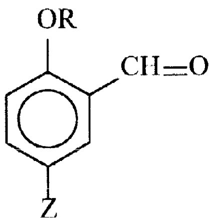
Abstract: Good yields of aldols, formed by reaction of the solvent acetone with some selected phenolic aldehydes, were obtained under Williamson arylmethyl ether conditions (Me_2SO_4 and K_2CO_3 in acetone). © 1998 Elsevier Science Ltd. All rights reserved.

The Williamson arylmethyl ether synthesis from phenols and Me_2SO_4, with anhydrous K_2CO_3 as base in dry acetone, is well recognized by organic chemists as one of the best procedures to achieve this conversion. Operational simplicity, high yields and clean reactions are the main advantages of this procedure.[2]

In this work we would like to present an unexpected reaction observed during a transformation of this sort, which although could be easily explained a posteriori, to our knowledge has not been reported previously.

O-Methylation of 5-bromosalicylaldehyde **1** under standard conditions (1.1 eqs. of Me_2SO_4 and 1.5 eqs. of solid K_2CO_3) in refluxing acetone for ≈ 2h, gave the expected methyl ether **2** in very high yield (95%).[3] However, under a longer period of time reflux (overnight, ≈ 15 h.) a new, more polar compound was obtained in 88% yield after flash column chromatography purification. A small amount (≈ 5%) of methyl ether **2** was also isolated from the less polar fractions in the chromatography.[4]



1, Z = Br, R = H
2, Z = Br, R = CH_3
3, Z = Cl, R = H
4, Z = NO_2 R = H

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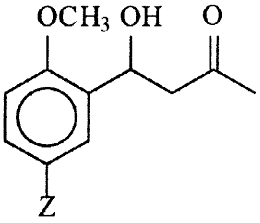
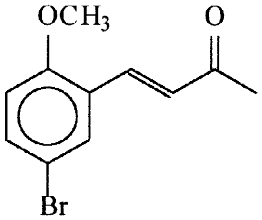
The new compound, obtained as a colorless crystalline solid (mp 56-57°, from ether-hexanes), analyzes correctly for $C_{11}H_{13}BrO_3$ (elemental analysis and HRMS)[5] and has a molecular weight of 273, as determined by chemical ionization MS. In the IR spectrum it shows strong absorption bands at 3450 (OH) and 1710 cm^{-1} (saturated C=O), and from the above data and the ^1H- and ^{13}C-NMR spectra, the structure **5** has been assigned to this new product.



5, Z = Br

6, Z = Cl

7, Z = NO_2



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^1H-NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.69 (dd, J_{AB} = 17.7, J_{AX} = 9.3, A part of a ABX system, 1 H), 2.91 (dd, J_{AB} = 17.7, J_{BX} = 3.0, B part of a ABX system, 1 H), 3.46 (d, $J_{CH\text{-}OH}$ = 4.2, exchanges with D_2O, OH), 3.80 (s, 3H), 5.36 (broad dt, J_{AX} = 9, $J_{BX} \approx J_{CH\text{-}OH}$ = 3-4, X part of a ABX system coupled with OH, 1H; this signal changes to dd after D_2O exchange), 6.72 (dd, J_o = 8.7, J_p = 0.6, H meta to aliphatic chain), 7.33 (dd, J_o = 8.7, J_m = 2.4, H para to aliphatic chain) and 7.59 (dd, J_m = 2.4, J_p = 0.6, H ortho to aliphatic chain).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 30.56, 50.06, 55.53, 64.64, 111.94, 113.35, 129.34, 130.88, 133.13, 154.66, 209.25.

The formation of the compound **5** under the above Williamson arylmethyl ether conditions can be easily explained as a K_2CO_3-catalyzed aldol condensation[6] of the solvent acetone with the methoxy aldehyde **2** initially obtained. According to this hypothesis, when aldehyde **2** was exposed to the methylation reaction conditions, but without Me_2SO_4 (1.5 eq. K_2CO_3, 17 h reflux in acetone), the aldol **5** was obtained in 83% yield.[7]

Phenolic aldehydes with the same substitution pattern, and a carbonyl electrophilicity close to **1** (e.g. **3** and **4**), also undergo the O-methylation-aldol condensation reactions with Me_2SO_4 and K_2CO_3 in acetone (15 and 9 h reflux, respectively) furnishing the corresponding methoxyaryl aldols **6** and **7** with excellent yields (89 % each).[8]

Aldols of the type reported here, have been long recognized as intermediates of Claisen-Schmidt condensations between aromatic aldehydes and acetone, and can be isolated under cold, dilute alkaline catalysis (NaOH, $Ba(OH)_2$).[9] However, yields are seldom reported at all, and in some cases they have been questioned.[10]

Hence, the high yields of aldols **5-7** reported in this paper under K_2CO_3 catalysis, suggest that the method can be of preparative value, at least in some cases.

Finally, a warning note about long time methylations of phenolic aldehydes with Me_2SO_4 and K_2CO_3 in acetone seems appropriate, since as mentioned above, the methoxyaryl aldehydes initially formed are prone to aldol condensation with the solvent[11].

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REFERENCES AND NOTES

1. Address for correspondence to this author at: Instituto de Química, UNAM Ciudad Universitaria, Coyoacán, 04510 México D.F., México. Contribution No. 1627 of Instituto de Química.
2. Deshayes, K. D. Potassium Carbonate. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Editor in chief; John Wiley & Sons: Chichester, 1995; vol. 6, pp. 4203-4205
3. Shapiro, H.; Smith, K. A. *J. Chem. Soc.* **1946**,143-144.
4. Actually, minor amounts of enone **8** and an unknown, dimeric bicyclic byproduct were also obtained. However, we have omitted them from the text for clarity in the discussion.
5. Elemental analysis (Galbraith Laboratories): Calculated for $C_{11}H_{13}BrO_3$: C, 48.37; H, 4.80; Br, 29.26. Found: C, 48.52; H, 4.94; Br, 29.16.

   HRMS: Calculated for $C_{11}H_{12}BrO_3$ (M^+ - 1): 272.0048. Found: 272.0050.
6. a) Nielsen, A. T.; Houlihan, W.J. The Aldol Condensation. In *Organic Reactions* **1968**, *16*, 1-438.

   b) Heathcock, C. H. The Aldol Reaction: Acid and General Base Catalysis. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds; Pergamon Press: Oxford, 1991; vol. 2, pp. 133-179.
7. 7% and 4% yields of enone **8** and aldehyde **2** were also obtained.
8. Aldol **6**: Oil. IR (film) 3432, 1710, 1488, 1247, 809, 644 cm^{-1}. ^{1}H-NMR ($CDCl_3$, MHz) δ 2.20 (s, 3H), 2.70 (dd, J_{AB} = 17.6, J_{AX} = 9.3, A part of a ABX system, 1H), 2.93 (dd, J_{AB} = 17.6, J_{BX} = 2.8, B part of a ABX system, 1H), 3.44 (broad d, $J_{CH\text{-}OH}$ = 4, OH, exchanges with D_2O), 3.80 (s, 3H), 5.37 (broad dt, J_{AX} = 9.2, $J_{BX} \approx J_{CH\text{-}OH}$ = 3-4, X part of a ABX system coupled with OH, 1H; this signal changes to dd after D_2O exchange), 6.77 (dd, J_o = 8.6, J_p = 0.6, H meta to aliphatic chain), 7.19 (dd, J_o = 8.6, J_m = 2.8, H para to aliphatic chain) 7.46 (dd, J_m = 2.8, J_p = 0.6, H ortho to aliphatic chain).

Aldol **7**: White prisms, mp 93-94° (acetone-hexanes). IR (KBr) 3460, 1707, 1591, 1511, 1487, 1343, 1268, 829 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.22 (s, 3H), 2.70 (dd, J_{AB} = 18, J_{AX} = 9.6, A part of a ABX system, 1H), 2.97 (dd, J_{AB} = 18, J_{BX} = 2.6, B part of a ABX system, 1H), 3.58 (d, J = 3.6, OH, exchanges with D_2O), 3.95 (s, 3H), 5.43 (broad dt, J_{AX} = 9.6, $J_{BX} \approx J_{CH\text{-}OH}$ = 2-3, X part of a ABX system, 1 H; this signal changes to dd after D_2O exchange), 6.93 (dd, J_o = 9, J_p = 0.7, H meta to aliphatic chain), 8.18 (dd, J_o = 9.0, J_m = 2.9, H para to aliphatic chain), 8.43 (dd, J_m = 2.9, J_p = 0.7, H ortho to aliphatic chain).

9. a) Baeyer, A.; Drewsen, V. *Ber.* **1882**, *15*, 2856-2864; b) Baeyer, A.; Becker, P. *Ibid.* **1883**, *16*, 1968-1971.

10. Tanasescu, I.; Georgescu, A. *Bull. Soc, Chim. Fr.* **1932**, *51*, 234-240. See also Table IX in reference 6a.

11. The procedure was as follows: A solution of 5-bromosalicylaldehyde (1.005 g., 4.9 mmol) and Me_2SO_4 (0.6 ml, 0.8 g., 6.3 mmol) in 30 ml. of dry acetone, containing anhydrous K_2CO_3 (1.06 g., 7.68 mmol) were heated in an oil bath at 55° for 15 h. The insoluble salts were filtered off and the solvent was removed at reduced pressure, leaving a green oil (1.516 g.) which was purified by flash chromatography in silica gel (hexanes - 15-30% AcOEt). The analytical sample of **5** was obtained by crystallization of the crude solid (1.202g., 88%) from Et_2O - hexanes, mp 56-57°.

    Aldols **6** and **7** were obtained by a similar procedure.

    The 5-bromosalicylaldehyde (Eastman), Me_2SO_4 (Aldrich, gold label) and anhydrous K_2CO_3 (Merck) were used as received. Although in our initial experiments the acetone was dried by refluxing for several days, first over anhydrous K_2CO_3 and then over anhydrous $CaSO_4$, we have found more recently that commercial acetone without any treatment works equally well.