An Improved Procedure for the Preparation of Acetals from Diaryl Ketones

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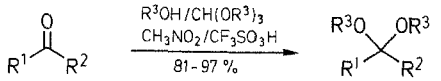
Acetals of diaryl ketones with nitro, halo and methoxy substituents are easily prepared in high yield by treatment with an alcohol and the corresponding trialkyl orthoformate in the presence of a catalytic amount of trifluoromethanesulfonic acid.

Acetals serve as important intermediates in organic synthesis. While dialkyl and arylalkyl ketone acetals are often easily prepared from their respective ketones, many acetals from diaryl ketones have been less accessible. The standard conditions for acetalization[1,2] often fail for diarylketones, making the desired compounds available only via indirect routes. Acetals of 4,4'-dichloro- and 4,4'-dimethoxybenzophenone, for example, are usually prepared by alkoxy-halogen exchange from the appropriate dihalodiarylmethanes.[3]

Acetal formation is strongly affected by electronic and steric factors. The rate determining step of acetalization is the formation of a cation from the protonated hemiacetal.[4] While the presence of two aryl groups should enhance the rate of acetalization by stabilizing the intermediate cation, the overall reaction may be more strongly affected by the steric crowding which would occur during initial hemiacetal formation. In order to compensate for the low rate of hemiacetal formation, the medium must be sufficiently acidic to promote effective protonation of any hemiacetal that is formed and sufficiently polar to allow stabilization of the cationic intermediate.

This communication describes conditions which allow for the direct transformation of a wide range of diaryl ketones into their respective dimethyl or diethyl acetals. The reaction is performed in general by the use of 10 mole equivalents of both the alcohol and its orthoformate equivalent, 0.2 mole equivalents of trifluoromethanesulfonic (triflic) acid, and nitromethane as the solvent. The scope of the new acetalization procedure is shown in the Table. All the acetals prepared, with the exception of **2c** and **2i**, are previously unreported. The products were generally obtained in excellent yield with no by-products. Fluorenone failed to give any acetal derivatives. When *p*-toluenesulfonic acid or a catalytic amount of sulfuric acid was substituted for the triflic acid the acetalization reactions proved either incomplete or entirely unsuccessful.



1 a-i **2 a-i**

1, 2	R^1	R^2	R^3
a	3-$O_2NC_6H_4$	3-$O_2NC_6H_4$	CH_3
b	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	CH_3
c	4-ClC_6H_4	4-ClC_6H_4	CH_3
d	4-ClC_6H_4	4-ClC_6H_4	C_2H_5
e	2-ClC_6H_4	2-ClC_6H_4	CH_3
f	4-FC_6H_4	4-FC_6H_4	CH_3
g	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CH_3
h	C_6H_5	4-$O_2NC_6H_4$	C_2H_5
i	C_6H_5	2-thienyl	CH_3

Table. Diaryl Ketone Diethyl and Dimethyl Acetals **2** Prepared

Product	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c] or Lit. mp (°C)	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)	MS (70 eV)[e] m/z (M^+–OR^3)
2a	92	126	$C_{15}H_{14}N_2O_6$ (318.3)	3.17 (s, 6H); 7.52 (t, 2H, J = 8.0); 7.28 (m, 4H); 8.15 (d, 2H, J = 7.8)	287
2b	91	144	$C_{15}H_{14}N_2O_6$ (318.3)	3.17 (s, 6H); 7.69 (d, 4H, J = 9.0); 8.19 (d, 4H, J = 9.0)	287
2c	87	74	68.5–70[3]	3.09 (s, 6H); 7.27 (d, 4H, J = 8.6); 7.40 (d, 4H, J = 8.6)	265, 267
2d	84	61	$C_{17}H_{18}Cl_2O_2$ (325.3)	1.2 (t, 6H, J = 7.0); 3.1 (q, 4H, J = 7.0); 7.2 (d, 4H, J = 7.1); 7.4 (d, 4H, J = 7.1)	281, 283
2e	92[f]	84	$C_{15}H_{14}Cl_2O_2$ (297.2)	3.07 (s, 6H); 7.2–7.35 (m, 6H); 8.21 (d, 2H, J = 7.4)	265, 267
2f	81	70	$C_{15}H_{14}F_2O_2$ (264.3)	3.09 (s, 6H); 6.98 (t, 4H, J = 8.6); 7.44 (dd, 4H, J = 8.6, 5.3)	233
2g	97	109	$C_{17}H_{20}O_4$ (288.3)	3.09 (s, 6H); 3.77 (s, 6H); 6.82 (d, 4H, J = 8.9); 7.38 (d, 4H, J = 8.9)	257
2h	91	oil	$C_{17}H_{19}NO_4$ (301.3)	1.24 (t, 6H, J = 7.0); 3.32 (q, 4H, J = 7.1); 7.26 (m, 3H); 7.47 (d, 2H, J = 7.0); 7.68 (d, 2H, J = 7.0); 8.09 (d, 2H, J = 7.0)	256
2i	93	57–59	59–60.5[5]	3.18 (s, 6H); 6.92 (m, 2H); 7.2–7.36 (m, 4H); 7.56 (dd, 2H, J = 8.3, 2.0)	203

[a] Yield of isolated product **2** based on **1**.
[b] Recrystallized from 95% ethanol.
[c] Satisfactory microanalysis obtained: C ±0.19, H ±0.15, N ±0.17; except **2h**: C +0.33, H −0.25.
[d] Recorded on a Varian XL-300 spectrometer.
[e] Recorded on a Finnegan MAT 1015 spectrometer using chemical ionization, NH_3 source.
[f] Product **2e** required a reflux time of 36 h.

Bis(3-nitrophenyl)dimethoxymethane (2a); Typical Procedure:
To a stirred solution of 3,3′-dinitrobenzophenone (2.00 g, 7.4 mmol), trimethyl orthoformate (7.80 g, 74.0 mmol), and MeOH (2.37 g, 74.0 mmol) in $MeNO_2$ (20 mL) cooled to 5 °C in an ice water bath triflic acid is added dropwise (220 mg, 1.5 mmol). The ice bath is replaced by an oil bath and the solution is heated at reflux for 4 h. After cooling to room temperature, the mixture is poured into a separatory funnel containing saturated $NaHCO_3$ solution (50 mL). The resulting mixture is extracted with ether (2 × 50 mL) and the organic phase dried ($MgSO_4$). Evaporation of the solvent under reduced pressure affords a white solid which is recrystallized from 95% ethanol; yield: 2.1 g (90%); mp 126 °C.

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