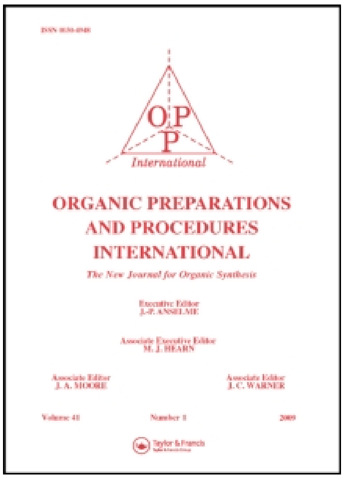

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AN ANOMALOUS HOUBEN-HOESCH REACTION AND SOME APPLICATIONS IN ARYLATION REACTIONS

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AN ANOMALOUS HOUBEN-HOESCH REACTION AND SOME APPLICATIONS IN ARYLATION REACTIONS

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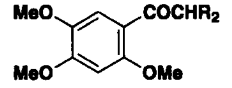
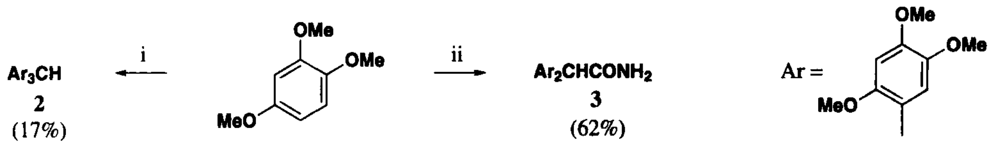
The Houben-Hoesch synthesis of ketones[1-3] from activated aromatic substrates and nitriles in the presence of HCl and $ZnCl_2$ has been reviewed by Ruske.[4] An abnormal Houben-Hoesch reaction of resorcinol with β-ketonitriles,[5] proceeds first *via* the keto group and then the nitrile to afford coumarins. This reaction falls within the scope of the von Pechmann reaction.[6] This communication reports a drastic deviation from the normal Houben-Hoesch reaction.

Since α,α-dichloro-2,4,5-trimethoxyacetophenone (**1a**), prepared *via* a Houben-Hoesch reaction between 1,2,4-trimethoxybenzene and dichloroacetonitrile, was very unreactive, failing to react with sodium acetate, methoxide and ethoxide even after prolonged reflux, the preparation of the keto acetal **1b** was attempted by a Houben-Hoesch reaction of 1,2,4-trimethoxybenzene with diethoxyacetonitrile. Instead of the expected **1b**, a 17% yield of a product with no carbonyl group in the IR and identified as tris(2,4,5-trimethoxyphenyl)methane (**2**),[7-9] was obtained. Evidently, the two ethoxy and the cyano groups of diethoxyacetonitrile were substituted by the aryl groups. This result prompted us to investigate other acetals. The reaction of trimethoxybenzene with diethoxyacetamide under the Houben-Hoesch conditions gave 2,2-bis(2,4,5-trimethoxy-phenyl)acetamide (**3**) in 62% yield. Since a possible intermediate in the formation of **3** is the benzylic ether **4**, it

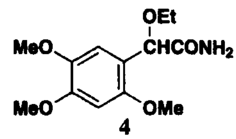


1a,b
a) R = Cl
b) R = OEt



i) $(EtO)_2CHCN$; ii) $(EtO)_2CHCONH_2$

was decided to employ other ethers, such as 2,2-dichloro-1-methoxy-1-(2,4,5-trimethoxyphenyl)ethane (**6**) as a starting compound in other reactions. The benzylic ether **6**, obtained by sodium borohydride reduction of ketone **1a** to the dichlorohydrin **5**, followed by the etherification with MeOH/H_2SO_4, was successfully arylated by both 1,2,4-trimethoxybenzene and 2,4-dimethoxychlorobenzene to give **8a** and **8b**, in 73% and 80% yields respectively. In these two reactions, the $ZnCl_2$/HCl mixture was successfully replaced by polyphosphoric acid (PPA).



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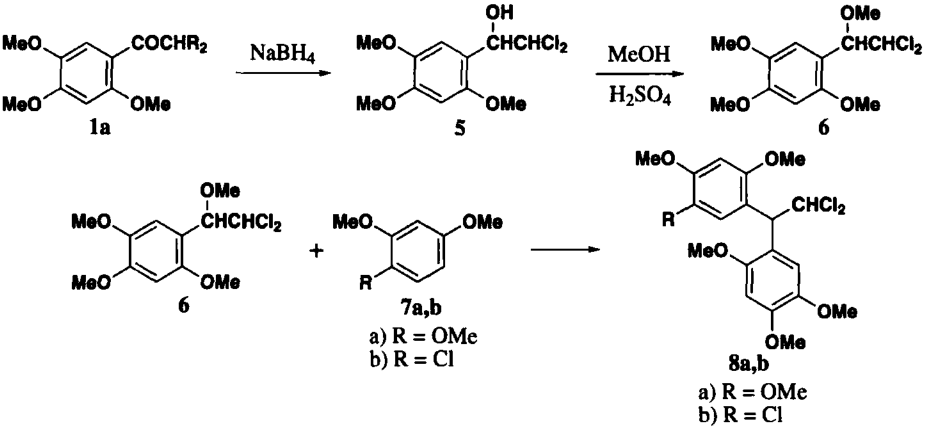
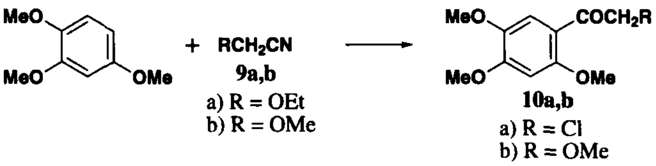


7a,b a) R = OMe b) R = Cl

8a,b a) R = OMe b) R = Cl

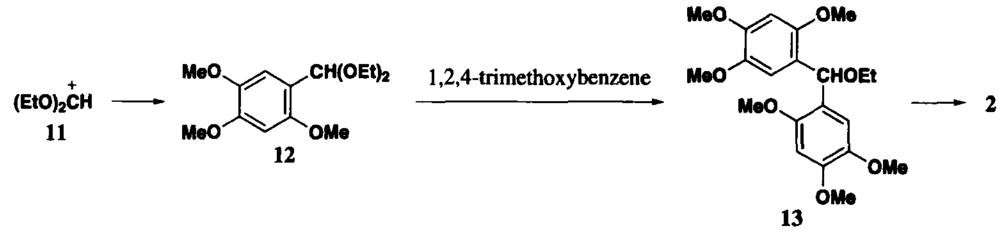
An attempt to prepare α-ethoxy-2,4,5-trimethoxyacetophenone (**10**, R = OEt) by a Houben-Hoesch reaction between 1,2,4-trimethoxybenzene and ethoxyacetonitrile (**9a**), gave the chloroketone **10a** instead of the expected ethoxy ketone. Surprisingly, the methoxy homologue **10b**, could be obtained from methoxyacetonitrile (**9b**) and 1,2,4-trimethoxybenzene under the Houben-Hoesch conditions, albeit in only 26% yield. The chloro ketone **10a** was obtained in 65% yield by reaction of 1,2,4-trimethoxybenzene with chloroacetonitrile.[10]



9a,b a) R = OEt b) R = OMe

10a,b a) R = Cl b) R = OMe

A possible rationalization of the reaction sequence leading to the formation of the triaryl compound **2** from diethoxyacetonitrile and 1,2,4-trimethoxybenzene may involve reaction of the resonance stabilized carbonium ion **11** with trimethoxybenzene to form compound **12** which, in a similar manner, reacts to yield the diaryl derivative **13**. Finally, this compound itself could also lose ethanol to give a very stable *bis*benzyl carbonium ion which then react to give **2**.



EXPERIMENTAL SECTION

Melting points were measured with a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded in a Perkin-Elmer FTIR-1600 spectrophotometer, using KBr wafers. The ^{1}H-NMR spectra (δ downfield from internal TMS) were obtained in a Varian Inova 300 spectrometer, in $CDCl_3$ as solvent, unless otherwise indicated. EI-MS data were acquired using a JEOL JMS-SX 102 A double-focusing instrument and a Finnigan Mat GCQ ion trap, with electron energy 70 eV. Elemental analysis were performed on a Fisons EA 1108 instrument.

α,α-Dichloro-2,4,5-trimethoxyacetophenone (1a).- In a 50 mL two-neck pear-shaped flask fitted with a gas-dispersion adapter and a reflux condenser with a $CaCl_2$ drying tube, containing anhydrous ether (10.5 mL), freshly melted $ZnCl_2$ (2.8 g, 20 mmol), 1,2,4-trimethoxybenzene (3.4 mL, 22 mmol) and dichloroacetonitrile (1.31 mL, 16 mmol), a current of dry HCl was passed for 2 h. The reaction mixture turned green and finally a heavy dark amber oil was formed and the reaction mixture was left 15 h at room temperature. The content was washed with ether (discarded) and poured into H_2O (100 mL). The precipitated solid was collected, mp 129-131°C and recrystallized from EtOH to give 3.77 g (83%) of straw colored needles, mp 131-132°C. IR (KBr): 1662, 1605, 1520, 1268, 1226, 1211, 1143, 1019 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3H), 4.00 (s, 6H), 6.50 (s, 1H), 7.13 (s, 1H), 7.43 ppm (s, 1H); CIMS *m/z* (%) M_1H^+ 279 (100), M_2H^+ 281 (64), M_3H^+ 283 (12).

Anal. Calcd. for $C_{11}H_{12}Cl_2O_4$: C, 47.30; H, 4.33. Found: C, 47.59; H, 4.10

tris(2,4,5-Trimethoxyphenyl)methane (2).- was obtained in analogous manner as **1a**, from anhydrous ether (5.1 mL), freshly melted $ZnCl_2$ (1.4 g, 10 mmol), 1,2,4-trimethoxybenzene (1.7 mL, 11 mmol) and diethoxyacetonitrile (0.76 mL, 5.5 mmol). Dry HCl was passed for 3 h. After 20 min the reaction mixture turned dark blue and 1 h later ether was added (1.5 mL). Work up as described above and crystallization from MeOH afforded 320 mg (17%) of a colorless solid, mp 182-184°C, *lit.*[9] 184-185°C. Its spectral data were identical to those of the literature.[7,8] Other components were recovered as a mixture of liquid reagents.

2,2-bis(2,4,5-Trimethoxyphenyl)acetamide (3).- was prepared as described for **1a**, from 1,2,4-trimethoxybenzene (1 mL, 6.7 mmol), diethoxyacetamide (494 mg, 3.35 mmol), $ZnCl_2$ (0.8 g, 5.8 mmol) in anhydrous ether (8 mL). Dry HCl was passed during 3.5 h and worked up as for **1a** to yield 810 mg (62%), of a colorless solid, mp 184-185°C (EtOH). One recrystallization from EtOH raised the mp to 185-186°C (white acicular prisms). IR (KBr): 3398, 1684, 1513, 1205, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.70 (s, 6H), 3.75 (s, 6H), 3.85 (s, 6H), 5.30 (s, 1H), 5.78 (s, 2H), 6.43 (s, 2H), 6.68 ppm (s, 2H); EIMS *m/z* (%) $M^{+\cdot}$ 391 (21), 347 (100), 181 (35).

Anal. Calcd. for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.11; H, 6.60; N, 3.44

2,2-Dichloro-1-(2,4,5-trimethoxyphenyl)ethanol (5).- To a suspension of the dichloro ketone **1a** (1 g, 3.6 mmol) in MeOH (6 mL), $NaBH_4$ (200 mg, 5.3 mmol) was gradually added. After complete dissolution, ether (75 mL) was added and the solution was washed with a saturated NaCl solution (5 x 10 mL). The dried (Na_2SO_4) ethereal solution was concentrated to an oil and benzene was added. Crystallization from benzene-hexane yielded 850 mg (84%) of white crystals, mp 88-90°C. IR (KBr): 3432, 1612, 1521, 1509, 1206, 1125, 1048, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.40 (d, 1H), 3.90 (s, 6H), 3.95 (s, 3H), 5.16 (t, 1H), 6.01 (d, 1H), 6.48 (s, 1H), 7.00 ppm (s, 1H); CIMS *m/z* (%) M_1H^+ 281 (32), M_2H^+ 283 (21), M_3H^+ 285 (5), 263 (100), 265 (64), 267 (12).

Anal. Calcd. for $C_{11}H_{14}Cl_2O_4$: C, 46.96; H, 5.02. Found: C, 47.23; H, 4.75

2,2,-Dichloro-1-methoxy-1-(2,4,5-trimethoxyphenyl)ethane (6).- To a solution of dichlorohydrin **5** (10 g, 35 mmol) in boiling MeOH (400 mL), was added conc. H_2SO_4 (2 mL) and the mixture was heated at reflux for 6 h. After cooling, the reaction mixture was diluted with water (200 mL) and left to crystallize. Another 200 mL of H_2O were added and the mixture was cooled in an ice-water bath. The precipitated product was collected, washed with cold water and dried to yield 9.4 g (90%) of white crystals, mp 92-93°C. IR (KBr): 1612, 1517, 1224, 1204, 1120, 1107, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.45 (s, 3H), 3.85 (s, 6H), 3.90 (s, 3H), 4.86 (d, 1H), 5.80 (d, 1H), 6.50 (s, 1H), 6.93 ppm (s, 1H); CIMS *m/z* (%) M_1H^+ 295 (26), M_2H^+ 297 (16), M_3H^+ 299 (3), 259 (100), 261 (33).

Anal. Calcd. for $C_{12}H_{16}Cl_2O_4$: C, 48.79; H, 5.46. Found: C, 48.91; H, 5.47

2,2-Dichloro-1,1-bis(2,4,5-trimethoxyphenyl)ethane (8a).- A mixture of the dichloro ether **6** (500 mg, 1.7 mmol), 1,2,4-trimethoxybenzene (0.25 mL, 1.67 mmol) and polyphosphoric acid (2 g) was heated (90°C) and stirred for 15 min. The reaction mixture was cooled and diluted with cold water. The separated blue solid was collected, dissolved in CH_2Cl_2 and decolorized with *Tonsil®* (an activated bleaching earth). After concentration and addition of ether, 530 mg (73%) of small white needles were obtained, mp 127-128°C. IR (KBr): 1609, 1516, 1464, 1208, 1033, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 6H), 3.83 (s, 6H), 3.86 (s, 6H), 5.20 (d, 1H), 6.56 (s, 2H), 6.82 (d, 1H), 7.12 ppm (s, 2H); CIMS *m/z* (%) M_1H^+ 431 (18), M_2H^+ 433 (13), M_3H^+ 435 (3), 395 (48), 263 (100), 265 (65), 267 (11).

Anal. Calcd. for $C_{20}H_{24}Cl_2O_6$: C, 55.66; H, 5.61. Found: C, 55.96; H, 5.80

2,2-Dichloro-1-(5-chloro-2,4-dimethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)ethane (8b).- Prepared as described for **8a**, in 80% yield as small white needles, mp 139-140°C (ether). IR (KBr): 1603, 1506, 1463, 1302, 1208, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (s, 6H), 5.10 (d, 1H), 6.46 (s, 1H), 6.49 (s, 1H), 6.70 (d, 1H), 7.00 (s, 1H), 7.41 ppm (s, 1H); CIMS *m/z* (%) M_1H^+ 435 (68), M_2H^+ 437 (66), M_3H^+ 439 (26), M_4H^+ 441 (7), 399

(100), 401 (65), 403 (16), 351 (63), 267 (68).

Anal. Calcd. for $C_{19}H_{21}Cl_3O_5$: C, 52.33; H, 4.86. Found: C, 52.60; H, 5.02

2,4,5-Trimethoxyphenacyl Chloride (10a).- Prepared as described for **1a** from 1,2,4-trimethoxybenzene and ethoxyacetonitrile, in 65% yield as white needles (MeOH), mp 166°C, *lit.*[10] 164-165°C (EtOH). IR (KBr): 1661, 1606, 1580, 1275, 1268, 1218, 1144, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H); 3.95 (s, 3H), 3.97 (s, 3H), 4.77 (s, 2H), 6.50 (s, 1H), 7.50 ppm (s, 1H); EIMS *m/z* (%) $M_1^{\cdot+}$ 244 (21), $M_2^{\cdot+}$ 246 (7), 195 (100).

α-Methoxy-2,4,5-trimethoxyacetophenone (10b).- Prepared from 1,2,4-trimethoxy-benzene (1.5 mL, 10 mmol), methoxyacetonitrile (0.75 mL, 10 mmol), freshly melted $ZnCl_2$ (1.2 g, 8.8 mmol) in anhydrous ether (8 mL). Dry HCl was passed for 3 h and the green oil which formed, solidified to a yellow solid. The reaction mixture was left at room temperature for 44 h in a closed flask to avoid HCl loss and then washed with ether (discarded), water (30 mL) was added to the residue and heated at 70°C for 10 min, with stirring. A white solid (625 mg, 26%), mp 130-133°C, separated upon cooling and stirring. Crystallization from MeOH afforded rectangular tablets, mp 131-132°C. IR (KBr): 1665, 1607, 1511, 1271, 1211, 1149, 1124, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.51 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.61 (s, 2H), 6.52 (s, 1H), 7.54 ppm (s, 1H); EIMS *m/z* (%) 240 (10), 195 (100).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.97; H, 6.71. Found: C, 59.68; H, 6.47

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