Synthesis of 1,1-Diaryl-2,2-dimethoxyethanes

Michael S. Ashwood, Lawrence A. Bell, Peter G. Houghton, Stanley H. B. Wright*

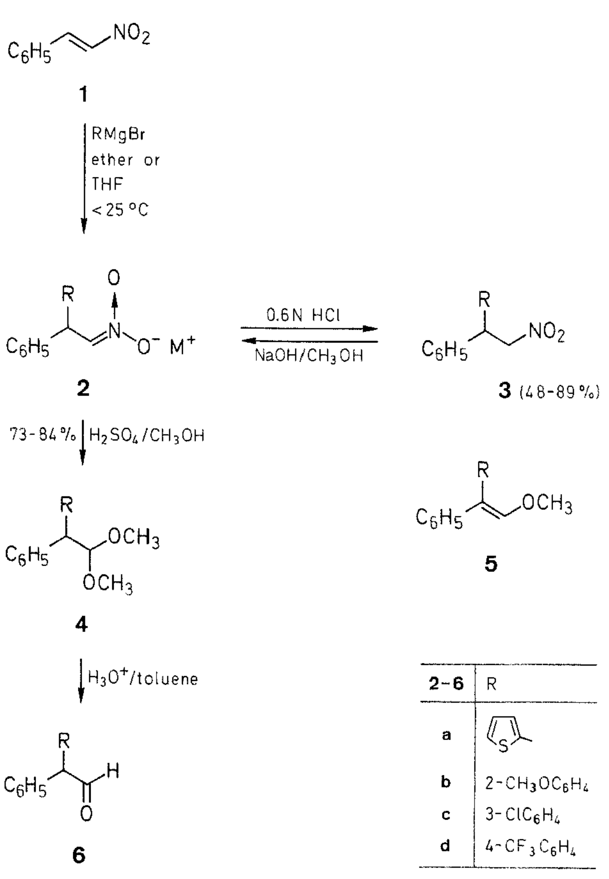
Merck Sharp and Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, England

The 1,4-additon of Grignard reagents to β-nitrostyrene to give 1,1-diaryl-2-nitroethanes and their subsequent conversion via a modified Nef reaction into 1,1-diaryl-2,2-dimethoxyethanes (diarylacetaldehyde dimethyl acetals) is described. The scope of the reaction has been briefly explored and one example demonstrated on a large scale.

During the course of our studies to develop a process for the large scale preparation of an enamide, we required a synthetic equivalent for the unstable acetaldehyde **6a**. The aldehyde may be prepared *in situ* by hydrolysis of the enol ether **5a** obtained by a Wittig reaction between 2-benzoylthiophene and methoxymethyltriphenylphosphonium chloride. This route to the enol ether suffered from certain disadvantages, including expensive starting materials, difficulty in purification and instability of the enol ether. These difficulties would be overcome by the use of the acetal **4a** available by solvolysis of the *aci*-anion **2a** using the modified Nef reaction of Jacobson,[1,2] and it was envisaged that the *aci*-anion could be prepared by 1,4-additon of a Grignard reagent to β-nitrostyrene.

Recent reviews of nitroalkene chemistry[3,4] have pointed out the usefulness of conjugate addition of enolate and lithium carbanions to nitroalkenes as a means of forming carbon-carbon bonds, which may be followed by further transformation of the nitroalkane products. However, initial reports[5,6] of attempted 1,4-addition reactions between monosubstituted nitroalkenes and Grignard reagents were not encouraging, the reactions being characterised by polymerisation of the nitroalkene and competing 1,2-addition reactions leading to very poor yields of product. Although an example[7] of the addition of an organocadmium reagent was a little more successful, the use of organocuprates[8] in the reaction gave inconsistent results. Interestingly Bartoli[8] recently observed that although aryl Grignard reagents and nitroarenes undergo 1,2 addition, alkyl Grignard reagents and mononitroarenes give products of 1,4 (and 1,6) conjugate addition.

We have found that by control of the exothermic reaction 1,4-addition of Grignard reagents to nitrostyrene, occurs smoothly at below room temperature in moderate to excellent yields. Thus reaction of thienyl magnesium bromide with β-nitrostyrene (**1**) occurred at < 25 °C in tetrahydrofuran to give a solution of the *aci*-anion **2a**, (M = MgBr) and addition of the solution to acidified methanol gave the crude acetal (**4a**). However, better results were obtained by first isolating and purifying the nitroethane **3a**. Optimisation of the reaction gave pure 1-nitro-2-phenyl-2-(2-thienyl)ethane (**3a**) in 89% yield in large scale (4 molar) reactions.



2-6	R
a	
b	2-$CH_3OC_6H_4$
c	3-ClC_6H_4
d	4-$CF_3C_6H_4$

The nitroalkane was dissolved in methanol containing sodium hydroxide pellets to give the *aci*-anion **2a**, (M = Na) which was quenched in acidified methanol at −10 °C to give, after an aqueous work-up, the crude acetal **4a** containing the aldehyde **6a** (5–15%). Before purification by distillation it was found to be advantageous to treat the crude mixture with methanolic

Table 1. Nitroalkanes 3 Prepared

Product	Yield (%)	mp (°C) or bp (°C)/ mbar	Molecular Formula[a]	CIMS[b] base peak; $(M-H)^-$ (%)	^{1}H-NMR (acetone-d$_6$/TMS)[c] δ, J (Hz)
3a	89	60–61	$C_{12}H_{11}NO_2S$ (233.3)	232 (100)	5.2 (m, 3H, $CHCH_2$); 6.8–7.3 (m, 8H_{arom})
3b	75	60–62	$C_{15}H_{15}NO_3$ (257.3)	46; 256 (28)	3.84 (s, 3H, OCH_3); 5.5 (m, 3H, $CHCH_2$); 6.8–7.6 (m, 9H_{arom})
3c	72	225/0.2[d]	$C_{14}H_{12}ClNO_2$ (261.7)	231; 260 (37); 262 (13)	5.00 (m, 1H, CH); 5.32 (m, 2H, CH_2); 6.8–7.3 (m, 9H_{arom})
3d	48	63–66	$C_{15}H_{12}F_3NO_2$ (295.3)	265; 294 (62)	5.09 (m, 1H, CH); 5.34 (m, 1H, CH); 5.37 (m, 1H, CH); 6.8–7.3 (m, 9H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.2, N ±0.3.

[b] Recorded on a V.G. Micromass 7070 spectrometer with ammonia gas as reagent.

[c] Recorded on a Bruker AM250 spectrometer.

[d] Kugelrohr distillation.

Table 2. Acetals 4 Prepared

Product	Yield (%)	bp (°C)/ mbar	Molecular Formula[a]	CIMS[b] base peak; $(M-H)^-$ (%)	^{1}H-NMR (acetone-d_6/TMS)[c] δ, J(Hz)
4a	84	140/0.1[d]	$C_{14}H_{16}O_2S$ (248.3)	185; 247 (56)	3.23 (s, 3H, OCH_3); 3.34 (s, 3H, OCH_3); 4.52 (d, 1H, J = 8, CH); 4.89 (d, 1H, J = 8, CH); 6.8–7.4 (m, 8H_{arom})
4b	76	200/0.2[e]	$C_{17}H_{20}O_3$ (272.4)	255; 271 (13)	3.19 (s, 3H, OCH_3); 3.20 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 4.7 (d, 1H, J = 8); 5.19 (d, 1H, J = 8, CH); 6.8–7.6 (m, 9H_{arom})
4c	82	200/0.2[e]	$C_{16}H_{17}ClO_2$ (276.8)	216; 245 (16)	3.25 (s, 3H, OCH_3); 3.26 (s, 3H, OCH_3); 4.33 (d, 1H, J = 8, CH); 5.14 (d, 1H, J = 8, CH); 6.8–7.3 (m, 9H_{arom})
4d	73	195/0.2[e]	$C_{17}H_{17}F_3O_2$ (310.3)	265; 309 (30)	3.32 (s, 6H, OCH_3); 4.43 (d, 1H, J = 8, CH); 5.21 (d, 1H, J = 8, CH); 7.1–7.6 (m, 9H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.2.

[b] Recorded on a V.G. Micromass 7070 spectrometer with ammonia gas as reagent.

[c] Recorded on a Bruker AM250 spectrometer.

[d] Leybold-Heraeus KDL4 still.

[e] Kugelrohr distillation.

hydrogen chloride to convert the unstable aldehyde into the acetal. In this way, pure 1,1-dimethoxy-2-phenyl-2-(2-thienyl)ethane (**4a**) containing small amounts of the enol ether **5a** was obtained in 84% yield.

Small scale reactions (0.05 molar) in diethyl ether as solvent gave the nitroalkanes **3b–d** in 48–75% yield, which were converted (0.02 molar reactions) into acetals **4b–d** in 73–82% yield.

1,1-Diaryl-2-nitroethanes 3; General Procedures:

Method A (for **3b–d**): The aryl bromide (0.07 mol) is added dropwise to Mg turnings (1.9 g, 0.07 mol) in dry ether (100 mL) at a rate to maintain a gentle reflux. After the addition is complete, the mixture is heated under reflux for 30 min and then cooled to 20 °C. The Grignard reagent solution is decanted from unreacted Mg and added dropwise to a solution of β-nitrostyrene (7.5 g, 0.05 mol) in dry ether (100 mL) maintained at 10–15 °C by an ice bath. The mixture is stirred for 1 h then 1 M HCl (110 mL) is added and the layers separated. The ether layer is washed with sat. aq. $NaHCO_3$ solution (100 mL), dried (Na_2SO_4), and evaporated to an oil which is purified by column chromatography on silica (CH_2Cl_2/cyclohexane). The pure nitroethanes are obtained by crystallisation from *i*-PrOH (compounds **3b** and **3d**) or distillation (compound **3c**). Yields range from 48 to 75% (Table 1).

Method B (for **3a**): A solution of 2-bromothiophene (635 g, 3.89 mol) in THF (950 mL) is added dropwise to a well stirred suspension of Mg turnings (106.4 g, 4.43 mol) in THF (1000 mL) maintaining a gentle reflux. After the addition is complete, the mixture is heated under reflux for a further 30 min before being cooled to 10 °C. A solution of β-nitrostyrene (525 g, 3.52 mol) in THF (1300 mL) is then added dropwise to the Grignard mixture, the temperature being maintained < 25 °C by cooling. When the addition is complete, the mixture is stirred for 30 min at room temperature. The mixture is treated with 5% aq. HCl acid (2.5 L) and then extracted with ether (2 × 750 mL). The combined organic layer is then washed with water (2 × 2.5 L) and finally sat. aq. $NaHCO_3$ solution (2.5 L), dried (Na_2SO_4) and evaporated to give a dark oil which solidifies. The dark solid is dissolved in hot *i*-PrOH (2.05 L), treated with charcoal at reflux, filtered and cooled to 0 °C for 2 h to give the nitroalkane **3a** as light tan solid; yield: 731 g (89%) mp 60–61 °C.

1,1-Dimethoxy-2-phenyl-2-(2-thienyl)ethane (4a); Typical Procedure:

A solution of the nitroethane (**3a**; 250 g, 1.07 mol) in MeOH (1250 mL) containing NaOH pellets (50 g, 1.25 mol) is stirred at room temperature for 30 min before being added dropwise to a mechanically stirred solution of conc. H_2SO_4 (650 mL) in MeOH (2.65 L) maintaining the temperature at −10 °C. When the addition is complete, the resulting dark solution is stirred at −10 °C for a further 1 h, before being added to a mixture of CH_2Cl_2 (2.5 L) and water (2.5 L). The aqueous layer is re-extracted with (2.5 L) and the combined organic layer is washed with sat. aq. $NaHCO_3$ solution (2.5 L), dried (Na_2SO_4), filtered through Hyflo (BDH Ltd.) and evaporated to give a brown/red oil. The oil is dissolved in MeOH (500 mL) and stirred with acetyl chloride (15 mL) for 30 min. The mixture is poured into sat. aq. $NaHCO_3$ (500 mL) and extracted with CH_2Cl_2 (700 mL). The aqueous layer is re-extracted with CH_2Cl_2 (500 mL), the organic layers combined, dried and evaporated to a brown oil. The oil is short-path distilled to give the acetal **4a** as a yellow oil; yield: 222.6 g (84%); bp 140 °C/0.1 mbar; GLC analysis: *acetal* **4a**, 93%; *enol ether* **5a**, 3%; and *nitroalkane* **3a**, 2%.

In other experiments compounds **4b–c** were obtained in a similar manner and the crude products distilled (Kugelrohr) without prior treatment with acetyl chloride in Yields range from 73–82% (Table 2).

Received: 2 October 1987; revised: 7 January 1988

(1) Jacobson, R.M. *Tetrahedron Lett.* **1974**, 3215.

(2) See also Jäger,V., Günther, H.J. *Angew. Chem.* **1977**, *89*, 253 *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 246.

(3) Barret, A.C.M., Graboski, G.C. *Chem. Rev.* **1986**, *86*, 751.

(4) Yoshikoshi, A., Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284.

(5) Kohler, E.P., Stone, J.F. *J. Am. Chem. Soc.* **1930**, *52*, 761.

(6) Buckley, G.D. *J. Chem. Soc.* **1947**, 1494.

(7) Cann, P.F., Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 1* **1974** 817.

(8) Bowlus, S.B. *Tetrahedron Lett.* **1975**, 3591.

(9) Bartoli, G. *Acc. Chem. Res.* **1984**, *17*, 109.