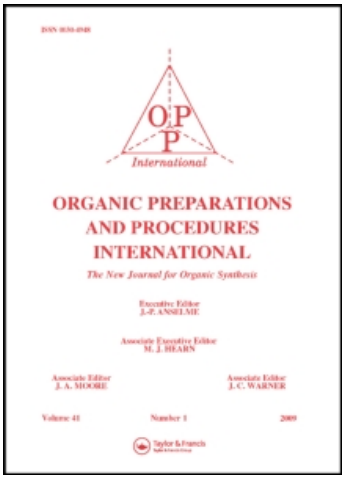

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A Practical Route for the Preparation of Aromatic *trans*-β-Nitroolefins

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Online publication date: 21 July 2010

To cite this Article Groszek, G.(2010) 'A Practical Route for the Preparation of Aromatic *trans*-β-Nitroolefins', Organic Preparations and Procedures International, 42: 4, 373 — 378
To link to this Article: DOI: 10.1080/00304948.2010.495680
URL: http://dx.doi.org/10.1080/00304948.2010.495680

Organic Preparations and Procedures International, 42:373–378, 2010

ISSN: 0030-4948 print
DOI: 10.1080/00304948.2010.495680

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A Practical Route for the Preparation of Aromatic *trans*-β-Nitroolefins

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Nitroalkenes are valuable precursors for a wide variety of target compounds.[1–4] They are powerful dienophiles in the Diels-Alder reaction and readily undergo addition reactions with many different nucleophiles.[5,6] Furthermore, they can be transformed into a variety of diverse functionalities.[7]

The standard method for the preparation of β-nitrostyrene is the reaction of benzaldehyde with nitromethane using sodium hydroxide (1 eq.) in methanol followed by acidification.[8] However, procedures and operations in this method are very tedious. Another approach is to condense aromatic aldehydes in benzene or toluene in the presence of amines to generate the nucleophile from the nitroalkane. The method involves heating the mixture for several hours using a Dean-Stark water trap to drive the reaction to completion. Another reagent system that has been used for the condensation of benzaldehyde with nitroalkanes is methylamine hydrochloride, potassium acetate and trimethyl orthoformate in methanol. This system serves as a water scavenger.[9] The most versatile preparation of nitroalkenes involves the Henry condensation of an aldehyde with a nitroalkane followed by dehydration of the resulting 2-nitroalcohol (*Scheme 1*). The Henry condensation is routinely carried out under basic conditions. The most commonly used bases are alkali metal alkoxides or hydroxides. Quaternary ammonium salts or metal complexes have also been utilized. The dehydration step requires a separate reagent.[4,9–11] For aryl aldehydes, it is difficult to avoid polymerization of the nitrostyrene derivatives[12,13] or/and of by-product formation due to Nef reaction. Thus the yields are relatively low. An interesting solution is to use organoamine-functionalized mesoporous catalysts, which helps control whether Henry or Knoevenagel products are obtained from aryl aldehydes and nitromethane.[14]

An alternate method for this type of condensation is hereby proposed. The products are easy to work-up and the procedure is quite general. The process involves K_2CO_3 and 18-crown-6 ether as a catalyst and the reaction is carried out at 12°C in 1,4-dioxane. Then, the

Received December 4, 2009.
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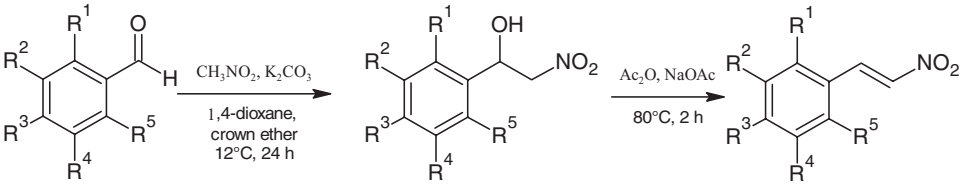
dehydration step is performed with acetic anhydride and sodium acetate without isolation of intermediate nitroalcohol derivatives (*Scheme 1*).



1a-g **2a-g**

a) $R^1 = R^2 = R^3 = R^4 = R^5 = H$; b) $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = NO_2$
c) $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = OMe$; d) $R^1 = OAc$, $R^2 = OMe$, $R^3 = R^5 = H$, $R^4 = NO_2$; e) $R^1 = OAc$, $R^2 = OMe$, $R^3 = R^4 = H$, $R^5 = NO_2$
f) $R^1 = OBn$, $R^2 = OMe$, $R^3 = R^4 = H$, $R^5 = NO_2$; g) $R^1 = OBn$, $R^2 = R^3 = H$, $R^4 = OMe$, $R^5 = NO_2$

Scheme 1

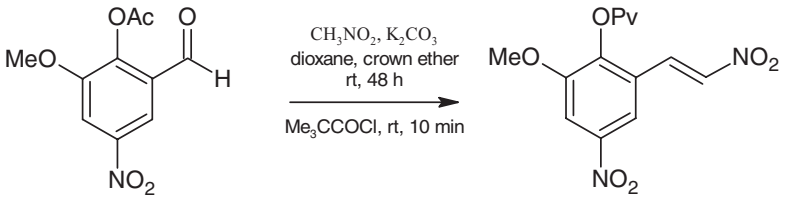
The scope of this method was extended to various substituted benzaldehydes **1a-g**. (*Table*) A relatively good yield of 65% was obtained with benzaldehyde. With *p*-anisaldehyde (**1c**), the yield was somewhat disappointing (41%). Nonetheless, this result is comparable to that reported by Cassel *et al.*[15] however, Gairaud *et al.*[16] was able to obtain this product in 65% yield. Most likely, the reason was that extensive subsequent polymerization of the nitrostyrene derivative was minimized, because weakly basic ammonium acetate was used in glacial acetic acid. For trisubstituted benzaldehydes **1d-g**, good yields in the range from 70 to 87% were obtained. These results suggest that electron-withdrawing groups in the aromatic ring favor the reaction. Although hydrolysis of the acetoxy groups of **1d** and **1e** did occur during the condensation step, the phenolic groups were evidently re-acetylated during the dehydration step. Indeed, when the condensation was performed with **1d** and **1e** without using acetic anhydride and sodium acetate, the deprotected products **3d** ($R_4 = NO_2$, $R_5 = H$) and **3e** ($R_4 = H$, $R_5 = NO_2$) were obtained in yields of 24% and 45%, respectively (*Scheme 2*).

1d, 1e **3d, 3e**

Scheme 2

When the condensation of **1d** was carried out with pivaloyl chloride, the *O*-pivalated nitrostyrene **4d** was obtained in yield of 50% (*Scheme 3*).

These last two transformations were not optimized.



1d **4d**

Scheme 3

The mechanism of the reaction might be viewed by assuming that potassium carbonate generates the nitronate ion, which exists as an ion pair with K^+. This salt is poorly soluble in the solvent, dioxane and 18-crown-6 ether are added to complex potassium ions, thus making the $^-CH_2NO_2$ ion sufficiently free to attack the carbonyl group of the aldehyde. However, the concentration of nitromethylene ion is still very low, and depends on the equilibrium of the system involving nitromethane and potassium carbonate on one end, and nitromethide potassium ion pair and potassium bicarbonate on the other. Elevated temperatures help to improve the solubility of nitromethylene potassium salt, but reduce the concentration of "naked" $^-CH_2NO_2$ ions which are less effectively separated from potassium ions by crown ether. Therefore, the reaction requires relatively low and constant temperature. Hence, the optimal conditions for this version of Henry condensation require a temperature of 12°C, a ten-fold molar excess of nitromethane and at least 24 hours for complete conversion. Additionally, potassium carbonate helps to keep the reaction environment anhydrous. In order to obtain the nitrostyrene, the nucleophilic addition has to be followed by dehydration with acetic anhydride and sodium acetate.

Table
Reaction of Aromatic Aldehydes with Nitromethane

	Product		Literature		
	Yield[a] (%)	mp. (°C)	Yield (%)	mp. (°C)	Ref.
2a	65	50–51 (DCM/hexane)	83	57–58 (EtOH)	8
			60	58–59 (MeOH)	16
				56–57 (EtOH)	17
2b	64	122–125 (DCM/hexane)	–	126 (EtOH)	17
			47	–––	18
2c	41[b]	83–85	35	86–87 (EtOH)	15
			65	86–87 (MeOH)	16
2d	70	167–168 (EtOAc/hexane)	–	–––	
2e	71	170–171 (EtOAc/hexane)	70	170–172	19
2f	87	118–120 (DCM/hexane)	91	119–120 (MeOH)	20
2g	82	158–161 (DCM/hexane)	82	158–161 (DCM/hexane)	21

[a]) Yield after crystallization.
[b]) Yield of crude product.

In conclusion, an effective variation of the Henry condensation that is particularly suitable for trisubstituted benzaldehyde has been developed. The active methylene compound was nitromethane in the presence of K_2CO_3 and 18-crown-6 ether in 1,4-dioxane.

Experimental Section

Melting points were determined on a Boëtius apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker (500 MHz) instrument in $CDCl_3$. Chemical shifts are expressed in δ with TMS as internal standard, coupling constants (J) are in Hz. IR and UV spectra were recorded on Perkin Elmer and Hewlett Packard 8453 instruments, respectively. Elemental analysis was performed on a AE 1108 Carlo Erba apparatus. Mass spectra were obtained on a AMD-604 spectrometer. TLC plates were silica gel 60 F_{254} Merck. Substrates **1a-c** and other materials were commercially available and compounds **1d** and **1e** were prepared according to literature procedures.[19] Compounds **1f** and **1g** had been previously prepared in our laboratory.[21]

General Procedure

Potassium carbonate (3.61 g, 0.026 mol) was suspended in 1,4-dioxane (100 mL) in a round bottom flask, equipped with a magnetic stir bar. Then, nitromethane (7.0 mL, 7.91 g, 0.13 mol) was added and the mixture was stirred for 10 min at room temperature. The reaction mixture was cooled to 12°C and kept for 1 h, then the aromatic aldehyde (0.013 mol) was added in the presence of 18-crown-6 ether (0.25 g, 0.9 mmol). The reaction progress was monitored by TLC (toluene-MeOH, 6:0.5). After 24 h, the solid (inorganic salts) was collected (and discarded), and then acetic anhydride (14 mL, 15.2 g, 0.15 mol) was added to the filtrate followed by addition of sodium acetate (250 mg) and the mixture was heated at 80°C for 2 h. The reaction mixture was poured into ice/H_2O mixture (1.5 L). The precipitate was collected and air-dried. The crude product was crystallized from appropriate solvents system to give nitroolefins **2**.

2-Acetoxy-3-methoxy-5-nitro-β-nitrostyrene (2d), mp. 167–168°C (EtOAc/hexane); $R_f = 0.5$ (toluene-MeOH, 5:1). IR (KBr): 3097, 1775 (C=O), 1646 (C=C), 1541, 1522, 1340 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, $J = 2.4$ Hz, 1 H, Ar*H*), 8.02 (d, $J =$ 13.8 Hz, 1 H, CH=C*H*NO_2), 7.91 (d, $J = 2.4$ Hz, 1 H, Ar*H*), 7.65 (d, $J = 13.8$ Hz, 1 H, C*H*=CHNO_2), 3.98 (s, 3 H, OCH_3), 2.45 (s, 3 H, C(O)CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.5 (C(O)*C*H_3), 56.9 (O*C*H_3), 109.4, 114.9, 125.1, 130.8, 140.5, 144.4, 146.2, 152.6, 167.2 (*C*(O)CH_3). MS (EI, 70 eV): *m/z* (%): 43 (100), 193 (15), 240 (6), 282 (1) $[M]^+$. HRMS-FAB, *m/z* $[M]^+$ Calcd for $C_{11}H_{10}N_2O_7$: 282.0488. Found: 282.0493. UV ($CHCl_3$), λ_{max} (ε): 282 nm (18900), (c = 0.10 mg/10 mL).

Anal. Calcd for $C_{11}H_{10}N_2O_7$: C, 46.82; H, 3.57; N, 9.93. Found: C, 46.95; H, 3.54; N, 10.02.

Condensation Procedure without Acetic Anhydride and Sodium Acetate

Condensation of **1d** and **1e** were performed as described above until complete conversion was achieved (TLC, toluene-MeOH, 4:1). Then reaction mixture was poured into cold water, the pH was adjusted to pH ~6 with conc. hydrochloric acid. The precipitated solid

was collected and air-dried and crystallized from ethyl acetate-hexane system solvents to give previously unreported nitroolefins **3d** and **3e** in yields of 24 and 45%, respectively.

2-Hydroxy-3-methoxy-5-nitro-β-nitrostyrene (3d), mp. 190–191°C (dec.) (EtOAc/hexane); $R_f = 0.3$ (hexane-EtOAc, 2:1). IR (KBr): 3288 (OH), 1617 (C=C), 1521, 1489, 1339, 1267 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 11.76 (s, 1H, O*H*), 8.35 (d, $J = 2.4$, 1H, Ar*H*), 8.28 (d, $J = 13.6$, 1H, CH=C*H*NO_2), 8.21 (d, $J = 13.6$, 1H, C*H*=CHNO_2), 7.82 (d, $J = 2.4$, 1H, Ar*H*), 3.98 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.6 (O*C*H_3), 108.4, 116.5, 119.1, 133.2, 139.4, 147.8 (2x*C*), 153.5. LRMS (EI, 70 eV) *m/z* [%]: 51 (6), 76 (6), 77 (8), 89 (6), 133 (14), 135 (14), 147 (26), 148 (6), 193 (100), 240 (M^+, 65). HRMS (EI), *m/z* $[M]^+$ Calcd for $C_9H_8N_2O_6$: 240.0382. Found: 240.0375. UV (EtOH), λ_{max} (ε): 463 (25500), 409 (24700), 316 (15300), (c = 0.07 mg/10 mL) nm.

2-Hydroxy-3-methoxy-6-nitro-β-nitrostyrene (3e), mp. 181–183°C (EtOAc/hexane); $R_f = 0.3$ (hexane-EtOAc, 2:1). IR (KBr): 3448 (OH), 1632, 1579, 1512, 1479, 1342, 1274 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.00 (s, 1H, O*H*), 8.23 (d, $J = 13.5$, 1H, CH=C*H*NO_2), 8.03 (d, $J = 13.5$, 1H, C*H*=CHNO_2), 7.73 (d, $J = 9.0$, 1H, Ar*H*), 7.25 (d, $J = 9.0$, 1H, Ar*H*), 3.98 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.7 (O*C*H_3), 111.4, 111.8, 117.7, 131.1, 141.2, 142.6, 147.3, 152.1. HRMS (ESI), *m/z* $[M+Na]^+$ Calcd for $C_9H_8N_2O_6Na$: 263.0275. Found: 263.0273. UV (CH_3CN), λ_{max} (ε): 279 (14000), 356 (7800), (c = 0.20 mg/10 mL) nm.

Condensation with Pivaloyl Chloride in Dehydration Step

A mixture of aldehyde **1d** (240 mg, 1.0 mmol), nitromethane (0.7 mL, 0.79 g, 1.3 mmol), potassium carbonate (155 mg, 1.12 mmol) and 18-crown-6 ether (30 mg) in dioxane (15 mL) was stirred at room temperature. The reaction progress was monitored by TLC (toluene-MeOH, 4:1). After 48 h, the reaction was complete, and then pivaloyl chloride (0.5 mL, 4 mmol) was added to reaction mixture. After 10 min reaction mixture was poured into water (100 mL), precipitate was collected and air-dried. The crude product was purified by column chromatography (silica gel, eluted hexane/EtOAc; 95:5) and crystallized from acetone to afford **4d** (165 mg, yield 50%).

3-Methoxy-2-pivaloyloxy-5-nitro-β-nitrostyrene (4d), mp. 191–192°C (acetone); $R_f = 0.6$ (hexane-EtOAc, 3:2). IR (KBr): 3099, 2976, 1761 (C=O), 1645, 1585, 1535, 1470, 1340, 1293 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, $J = 2.4$, 1H, Ar*H*), 7.99 (d, $J = 13.8$, 1H, CH=C*H*NO_2), 7.89 (d, $J = 2.4$, 1H, Ar*H*), 7.65 (d, $J = 13.8$, 1H, C*H*=CHNO_2), 3.96 (s, 3H, OCH_3), 1.45 (s, 9H, 3xCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.1 (3x*C*H_3), 39.6, 56.9 (O*C*H_3), 109.3, 114.8, 125.2, 130.7, 140.4, 145.0, 146.0, 152.7, 175.1 (*C*=O). LRMS (EI, 70 eV) *m/z* [%]: 324 (M^+, 1), 240 (14), 194 (7), 193 (61), 147 (15), 135 (6), 85 (23), 76 (5), 57 (100), 41 (9). HRMS (EI), *m/z* $[M]^+$ Calcd for $C_{14}H_{16}N_2O_7$: 324.0958. Found: 324.0966. UV (CH_3CN), λ_{max} (ε): 283 (21100), (c = 0.07 mg/10 mL) nm.

Anal. Calcd for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 51.80; H, 4.98; N, 8.63.

Acknowledgment

This project was supported by Polish Ministry of Scientific Research and Information Technologies, Grant no. 2 P05F 010 28.

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