Canadian Journal of Chemistry
Revue canadienne de chimie

Michael addition at neutral pH: A facile synthesis of 1,3-dinitroalkanes

Journal:	<i>Canadian Journal of Chemistry</i>
Manuscript ID	cjc-2017-0257.R2
Manuscript Type:	Article
Date Submitted by the Author:	01-Aug-2017
Complete List of Authors:	Bora, Porag; North Eastern Hill University Bora, Pranjal; nehu, chemistry; nehu, chemistry Wahlang, Barisha; North Eastern Hill University, Chemistry Bez, Ghanashyam; North Eastern Hill University, Chemistry
Is the invited manuscript for consideration in a Special Issue?:	N/A
Keyword:	1, 3-Dinitroalkanes, Michael addition, phosphate buffer, base-free, diastereoselective

SCHOLARONE™
Manuscripts

Michael addition at neutral pH: A facile synthesis of 1,3-dinitroalkanes

Porag Bora, Pranjal P Bora, Barisha Wahlang and Ghanashyam Bez*

Department of Chemistry, North Eastern Hill University, Shillong-793022, India

ghanashyambez@yahoo.com

Abstract: Base catalyzed Michael addition of nitroalkane to conjugated nitroalkene suffers serious practical difficulties due to the formation of oligomeric byproduct. Given its importance for synthesis of pharmacologically relevant organic compounds, a scalable synthesis of 1,3-dinitroalkane is developed by addition of nitroalkane to nitroalkene in aqueous phosphate buffer at pH 7.0 with no added traditional base catalyst.

Keywords: 1, 3-Dinitroalkanes; Michael addition; phosphate buffer; base-free, diastereoselective

Introduction

In organic synthesis, methods for the development of carbon-carbon bond forming reactions are considered as the cornerstone of building complex molecular architecture.¹⁻⁵ Many of such C-C bond forming reactions are the results of reaction between carbanions and an electrophile. Among the carbanions, nitro-stabilized carbanions have an advantage over others due to their easier generation and requirement of a less sophisticated reaction environment. In fact, there is no structural moiety that is more efficient than nitroalkanes due to its versatile reactivity profile⁶⁻⁸ which makes them ideal synthetic precursors amenable to functional as well as structural diversifications.⁹ One such rapidly emerging class among the its rank is 1,3-dinitroalkanes that works as a starting material for the synthesis of pharmaceutically important 1,3-diamines,¹⁰⁻¹¹ polyfunctionalized carbacycles¹²⁻¹⁴ and bicycle[3.3.1]nonanes,¹⁵ highly substituted arenes¹⁶⁻¹⁸ and phenols.¹⁹ Although conjugate addition of nitroalkanes to nitroalkenes generates 1, 3-dinitro compounds, the sensitivity of the nitroalkanes towards acid and base makes it a difficult reaction to deal with. Therefore, control of pH is the key to most of the nitroalkane addition reactions to nitroalkene which often gives polymeric byproducts resulting in low reaction yields. Especially in the synthesis of 1, 3-dinitro compounds by Michael addition nitroalkanes with nitroalkenes, the suppression of the unfavored subsequent oligomerization under basic conditions is extremely difficult.²⁰ To avoid the formation of the undesired byproducts, many mild catalytic system such as triphenylphosphine,²¹ DBU²² have found application. Recently, Baron et al. carried out Michael addition of various active methylene compounds with β -nitroindoles using solid potassium carbonate or sodium acetate as a base under ultrasonication.²³ Recently, we reported that nitroalkanes undergo the Henry reaction with aldehydes in phosphate buffer at neutral pH to provide β -nitroalcohols in excellent yield.²⁴ Given the complications

attached to the base catalyzed synthesis of 1,3-dinitroalkanes and their perceived importance as versatile building blocks, the development of a synthetic methodology devoid of traditional base catalysts may help circumvent the problem of oligomerization. We also envisaged that the use of neutral phosphate buffer in aqueous medium will eliminate the formation of oligomeric byproducts due to the poor solubility of the more hydrophobic 1,3-dinitroalkane in aqueous medium. To the best of knowledge, no report on the addition of nitroalkanes to nitroolefins in the absence of a basic medium has been reported in the literature. Therefore, we wish to report our findings on the addition of nitroalkanes to β -nitrostyrene derivatives at neutral pH to successfully synthesize 1,3-dinitropropanes (Scheme 1).

Scheme 1. Synthesis of 1,3-dinitro compounds

Experimental

General remark

All the products were characterized by ^1H NMR, ^{13}C NMR spectroscopy. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a Bruker AC-400 using CDCl_3 as solvent and TMS as internal standard, unless otherwise stated. Mass spectra were obtained on a Waters ZQ 4000 mass spectrometer by the ESI method, while the elemental analyses of the complexes were performed on a Perkin–Elmer-2400 CHN/S analyzer. HPLC analysis were performed on Waters M515 series equipped with a chiral column (detailed for each compound below), using mixtures of *n*-hexane/isopropyl alcohol (IPA) as mobile phase, diastereoselectivity was determined by HPLC analysis of the crude products using chiral columns in comparison with the racemic materials. For column chromatography, we employed Merck silica gel 60-120 mesh.

92 Preparation of phosphate buffer²⁵

93 A 0.2 M stock solution of A was prepared by dissolving 27.6 g of monosodium phosphate
94 monohydrate in water to make a 1000 mL solution, while 1000 mL of 0.2 M stock solution of B
95 was prepared by dissolving 53.6 g of dibasic sodium phosphate heptahydrate in water. Then 100
96 mL of 0.4 M stock solution of phosphate buffer at pH 7 was prepared by mixing 39 mL of stock
97 solution A and 61 mL of the stock solution B.

98

99 Typical procedure

100 Aqueous phosphate buffer solution (pH 7.0, 0.5 mL) was added to a round-bottomed flask
101 containing a mixture of (*E*)-(2-nitrovinyl)benzene (37 mg, 0.25 mmol) and nitromethane (30 mg,
102 0.50 mmol). After vigorous stirring at 60 °C for the specified time, the reaction was complete.
103 The reaction mixture was extracted with ethyl acetate (3×15 mL), The combined organic phases
104 was dried over anhydrous sodium sulfate, evaporated under reduced pressure, and the resulting
105 mixture was purified by column chromatography (ethyl acetate/hexane 1:9) to obtain the pure
106 product.

107

108 Spectral data

109 **1,3-Dinitro-2-phenylpropane (1a).**²⁶ 90% yield; yellow gum; IR (KBr): 2917, 1551, 1492,
110 1427, 1371 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 4.22–4.33 (m, 1 H), 4.69–4.82 (m, 4 H), 7.17–
111 7.20 (m, 2 H), 7.22–7.38 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ = 42.0, 77.0, 127.6, 129.3,
112 129.7, 134.5 MS (ESI): m/z = 233 [M + Na]⁺; Anal. Calcd. (%) for C₉H₁₀N₂O₄: C 51.43, H 4.80,
113 N 13.33; Found (%): C 51.37, H 4.79, N 13.38.

114 **1,3-Dinitro-2(4-fluorophenyl)propane (1b):** 90% yield; yellow solid; m.p. 84-86 °C, IR (KBr):
115 2917, 1553, 1495, 1429, 1372 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.28- 4.35 (quintet, *J* = 7.2
116 Hz, 1 H), 4.70- 4.81 (m, 4 H), 7.06- 7.10 (m, 2 H), 7.20-7.23 (m, 2 H) ppm; ¹³C NMR (100 MHz,
117 CDCl₃): δ = 41.0, 76.7, 116.5 (d, *J* = 21.7 Hz), 129.2 (d, *J* = 8.6 Hz), 129.9 (d, *J* = 3 Hz), 164 (d, *J*
118 = 247 Hz), ppm; MS (ESI): *m/z* = 252 [M + Na]⁺; Anal. Calcd. (%) for C₉H₉FN₂O₄: C 47.37, H
119 3.98, N 12.28; Found (%): C 47.31, H 3.97, N 12.32.

120 **1,3-Dinitro-2(4-chlorophenyl)propane (1c):**²⁷ 82% yield; Yellow solid; mp 77-79 °C; IR
121 (KBr): 2924, 1563, 1559, 1384, 825 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.27-4.34 (quintet, *J*
122 = 7.2 Hz, 1 H), 4.70-4.80 (m, 4 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H) ppm; ¹³C
123 NMR (100 MHz, CDCl₃): δ = 41.1, 76.5, 128.7, 129.8, 132.6, 135.2 ppm; MS (ESI): *m/z* = 267
124 [³⁵M + Na]⁺, 269 [³⁷M + Na]⁺; Anal. Calcd. (%) for C₉H₉ClN₂O₄: C 44.19, H 3.71, N 11.45;
125 Found (%): C 44.11, H 3.69, N 11.50.

126 **1,3-Dinitro-2(4-bromophenyl)propane (1d):**²⁸ 78% yield; colourless liquid; IR (KBr): 2924,
127 1561, 1548, 1386, 1373 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.19-4.26 (m, 1 H), δ 4.63-4.74
128 (m, 4 H), δ 7.04 (d, *J*=8.4 Hz, 2 H), δ 7.44 (d, *J*=8.4 Hz, 2 H) ppm; ¹³C NMR (100 MHz, CDCl-
129 3): δ = 36.8, 75.7, 126.1, 128.5, 130.1, 134.1 ppm; MS (ESI): *m/z* = 311 [⁷⁹M + Na]⁺, 313 [⁸¹M +
130 Na]⁺; Anal. Calcd. (%) for C₉H₉BrN₂O₄: C 37.39, H 3.14, N 9.69; Found (%): C 37.44, H 3.13, N
131 9.74.

132 **1,3-Dinitro-2(2-nitrophenyl)propane (1e):** 90% yield; brown gum; IR (KBr): 2924, 1561,
133 1549, 1429, 1377 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ = 4.44- 4.51 (quintet, *J* = 7.2 Hz, 1H),
134 4.80- 4.90 (m, 4H), 7.57-7.67 (m, 2H), 8.15- 8.21 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ
135 = 41.2, 76.0, 122.4, 124.1, 130.7, 133.9, 136.5, 148.7 ppm; MS (ESI): *m/z* = 256 [M+H]⁺; Anal.
136 Calcd. (%) for C₉H₉N₃O₆: C 42.36 H, 3.55, N 16.47; Found (%): C 42.33, H 3.54, N 16.55.

1,3-Dinitro-2(3-nitrophenyl)propane (1f):²⁷ 93% yield; brown gum; IR (KBr): 2921, 1559, 1548, 1431, 1375 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.44- 4.51 (m, 1 H), 4.80- 4.90 (m, 4 H), 7.59- 7.62 (m, 2 H), 8.16 (s, 1 H), 8.23- 8.25 (m, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 40.2, 75.0, 121.4, 123.2, 129.8, 132.8, 135.3, 147.7 ppm; MS (ESI): m/z = 256 [M + H]⁺; Anal. Calcd. (%) for C₉H₉N₃O₆: C 42.36, H 3.55, N 16.47; Found (%): C 42.40, H 3.54, N 16.41.

1,3-Dinitro-2(4-methylphenyl)propane (1g):²⁹ 81% yield; brown solid; m.p. 47-49 °C; IR (KBr): 2923, 1563, 1551, 1380, 815 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.34 (s, 1 H), 4.24- 4.32 (quintet, *J* = 7.2 Hz, 1 H), 4.71- 4.80 (m, 4 H), 7.10 (d, *J* = 7.6 Hz, 2 H), 7.20 (d, *J* = 7.6 Hz, 2 H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 21.0, 41.4, 77.3, 127.2, 130.2, 131.0, 139.0 ppm; MS (ESI): m/z = 247 [M + Na]⁺; Anal. Calcd. (%) for C₁₀H₁₂N₂O₄: C 53.57, H 5.39, N 12.49; Found (%): C 53.38, H 5.41, N 12.57.

1,3-Dinitro-2(2-methoxyphenyl)propane (1h): 80% yield; brown gum; IR (KBr): 2925, 1565, 1548, 1393, 1371, 1253 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 3.87 (s, 3H), 4.42-4.49 (m, 1 H), 4.85 (d, *J* = 7.2 Hz, 4 H), 6.91-6.95 (m, 2 H), 7.13 (d, *J* = 6.8 Hz, 1 H), 7.30 (t, *J* = 8 Hz, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 39.2, 55.5, 75.3, 111.3, 121.3, 122.0, 130.0, 130.3, 157.0 ppm; MS (ESI): m/z = 241 [M + H]⁺; Anal. Calcd. (%) for C₁₀H₁₂N₂O₅: C 50.00, H 5.04, N 11.66; Found (%): C 49.89, H 5.03, N 11.71

1,3-Dinitro-2(4-methoxyphenyl)propane (1i):²⁶ 84% yield; brown gum; IR (KBr): 2921, 1562, 1550, 1386, 1372, 1244 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 3.78 (s, 3 H), 4.22- 4.29 (m, 1H), 4.68-4.78 (m, 4 H), 6.87 (d, *J* = 8.0 Hz, 2 H), 7.12 (d, *J* = 8.0 Hz, 2 H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 41.1, 55.3, 76.9, 114.9, 128.5, 159.9 ppm; MS (ESI): m/z = 241 [M+H]⁺; Anal. Calcd. (%) for C₁₀H₁₂N₂O₅: C 50.00, H 5.04, N 11.66; Found (%): C 50.10, H 5.05, N 11.73.

160 **1,3-Dinitro-2(3,4-methylenedioxyphenyl)propane (1j):**²⁹ 77% yield; brown gum; IR (KBr):
161 2920, 1563, 1548, 1443, 1393, 1249, 1044 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.19 (quintet, J
162 = 7.2 Hz, 1 H), 4.67-4.76 (m, 4 H), 5.97 (s, 2 H), 6.67 (d, J = 5.2 Hz, 1 H), 6.77 (d, J = 8.8 Hz, 2
163 H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 41.5, 76.8, 101.6, 107.5, 107.5, 109.1, 121.0, 127.4,
164 148.0, 148.5; MS (ESI): m/z = 277 [M+Na]⁺; Anal. Calcd. (%) for C₁₀H₁₀N₂O₆: C 47.25, H 3.97,
165 N 11.02; Found (%): C 47.11, H 3.99, N 11.11.

166 **1,3-Dinitro-2(1-naphthyl)propane (1k):**²⁹ 82% yield; brown gum; IR (KBr): 2923, 1567, 1551,
167 1390, 1371, 810 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.88-4.98 (m, 4 H), 5.23-5.30 (m, 1 H),
168 7.32 (d, J = 7.6 Hz, 1 H), 7.44 (t, J = 8 Hz, 1 H), 7.56 (t, J = 7.2 Hz, 1 H), 7.64 (m, 1 H), 7.85 (d,
169 J = 8.8 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 8.18 (d, J = 8.4 Hz, 1 H) ppm; ¹³C NMR (100 MHz,
170 CDCl₃): δ = 36.2, 76.2, 121.5, 123.8, 125.2, 126.5, 127.6, 129.5, 129.7, 129.9, 130.6, 134.3 ppm;
171 MS (ESI): m/z = 283 [M+Na]⁺; Anal. Calcd. (%) for C₁₀H₁₂N₂O₅: C 60.00, H 4.65, N 10.76;
172 Found (%): C 59.77, H 4.66, N 10.79.

173 **1,3-Dinitro-2(2-furyl)propane (1l):**²⁹ 85% yield; yellow gum; IR (KBr): 2930, 1555, 1543,
174 1378 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.44 (q, J = 6.4 Hz, 1 H), 4.80 (d, J = 6.4 Hz, 4 H),
175 6.27 (d, J = 2.8 Hz, 1H), 6.34 (d, J = 1.6 Hz, 1H), 7.39 (s, 1 H) ppm. ¹³C NMR (100 MHz,
176 CDCl₃): δ = 35.8, 74.5, 108.9, 110.8, 143.4, 147.0 ppm. MS (ESI): m/z = 223 [M+Na]⁺; Anal.
177 Calcd. (%) for C₇H₈N₂O₅: C 42.01, H 4.03, N 14.00; Found (%): C 42.18, H 4.02, N 14.06.

178 **1-Nitro-2-(nitromethyl)pentane (1m):**²⁶ 80% yield; yellow gum; IR (KBr): 2920, 1561, 1550,
179 1393 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 0.91 (t, J = 6.8 Hz, 3 H), 1.38-1.46 (m, 4 H), 2.87
180 (q, J = 6.0 Hz, 1 H), 4.46 (dd, J = 13.2 Hz, 8 Hz, 2 H), 4.55 (dd, J = 13.6 Hz, 7.2 Hz, 2 H) ppm;
181 ¹³C NMR (100 MHz, CDCl₃): δ = 13.6, 19.5, 31.0, 35.7, 76.0 ppm; MS (ESI): m/z = 177

182 $[M+H]^+$; Anal. Calcd. (%) for $C_6H_{12}N_2O_4$: C 40.91, H 6.87, N 15.90, Found (%): C 40.86, H
183 6.89, N 15.79.

184 **3-Phenyl-2,4-dinitrobutane (1n):**³¹ 80% yield; reddish brown gum; IR (KBr): 2933, 1557,
185 1550, 1374 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, J = 6.4 Hz, 3 H), 1.51 (d, J = 6.8 Hz,
186 3 H), 3.97-4.00 (m, 1 H), 4.61 (dd, J = 13.2, 8.8 Hz, 1 H), 4.76-4.94 (m, 3 H), 7.14-7.18 (m, 2 H),
187 7.30-7.32 (m, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7, 17.8, 47.3, 47.7, 76.1, 76.8,
188 84.2, 84.6, 128.0, 129.0, 129.2, 129.5, 133.1, 133.7 133.9 ppm; The product was analyzed to
189 determine the diastereoselectivity of the reaction. The diastereoselectivity (70:30 d.r.) of the
190 reaction were determined by HPLC analysis using a CHIRALPAK AS column, hexane/2-
191 propanol 40:10, flow rate 0.5 mL/min, UV 210 nm, major diastereomer: 25.2, 27.0 min; minor
192 diastereomer: 20.0, 22.4 min. MS (ESI): m/z = 247 $[M + Na]^+$; Anal. Calcd. (%) for $C_{10}H_{12}N_2O_4$:
193 C 53.57, H 5.39, N 12.49; Found (%): C 53.67, H 5.38, N 12.55.

194 **3(4-Fluorophenyl)-2,4-dinitrobutane (1o):**³² 80% yield; white solid, m.p. 125- 128 °C. IR
195 (KBr): 2928, 1560, 1495, 1433, 1383 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (d, J = 6.4
196 Hz, 3 H), 1.58 (d, J = 6.4 Hz, 3 H), 3.97- 4.02 (m, 1 H), 4.76 (dd, J = 13.6 Hz, 4.8 Hz, 1 H),
197 4.88- 4.96 (m, 3 H), 7.02- 7.07 (m, 2 H), 7.12-7.15 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$):
198 δ = 16.8, 46.7, 76.2, 84.0, 116.3 (d, J = 21.1 Hz), 129.7 (d, J = 2.7 Hz), 129.8 (d, J = 7.4 Hz),
199 164.1 (d, J = 247 Hz) ppm. The product was analyzed to determine the diastereoselectivity of the
200 reaction. The diastereoselectivity (97:3 d.r.) of the reaction were determined by HPLC analysis
201 using a CHIRALCEL OD-H column, hexane/2-propanol 44:6, flow rate 0.5 mL/min, UV 210
202 nm, major diastereomer: 58.0, 73.6 min; minor diastereomer: 46.2, 48.8 min. MS (ESI): m/z =
203 265 $[M + Na]^+$; Anal. Calcd. (%) for $C_{10}H_{11}FN_2O_4$: C 49.59, H 4.58, N 11.57; Found (%): C
204 49.64, H 4.59, N 11.60.

205 **3(4-Chlorophenyl)-2,4-dinitrobutane (1p):**³³ 82% yield; yellow solid; IR (KBr): 2930, 1563,
206 1556, 1390, 823 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 1.40 (d, *J* = 7.6 Hz, 3 H), 1.56 (d, *J* =
207 6.8 Hz, 3 H), 3.96-4.01 (m, 1 H), 4.62 (dd, *J* = 13.2, 8.0 Hz, 1 H), 4.75 (m, 1 H), 4.86-4.94 (m, 2
208 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ =
209 16.8, 17.8, 46.8, 47.1, 76.0, 76.5, 83.9, 84.3, 129.3, 129.5, 129.8, 132.0, 135.1 ppm. The product
210 was analyzed to determine the diastereoselectivity of the reaction. The diastereoselectivity (89:11
211 d.r.) of the reaction were determined by HPLC analysis using a CHIRALPAK AS column,
212 hexane/2-propanol 95:5, flow rate 1.0 mL/min, UV 210 nm, major diastereomer: 41.5, 48.0 min;
213 minor diastereomer: 32.3, 48.0 min. MS (ESI): *m/z* = 281 [M + Na]⁺; Anal. Calcd. (%) for
214 C₁₀H₁₁ClN₂O₄: C 46.43, H 4.29, N 10.83; Found (%): C 46.49, H 4.28, N 10.87.

215 **3(2-Nitrophenyl)-2,4-dinitrobutane (1q):**³¹ 89% yield; brown gum, IR (KBr): 2933, 1565,
216 1549, 1393 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 1.60 (d, *J* = 6.8 Hz, 3 H), 1.71 (d, *J* = 6.8 Hz,
217 3 H), 4.75-4.76 (m, 1 H), 4.91-5.05 (m, 2 H), 5.25-5.32 (m, 1 H), 7.36 (d, *J* = 7.2 Hz, 1 H), 7.53-
218 7.65 (m, 2 H), 7.96 (d, *J* = 8.0 Hz, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 17.1, 18.1, 41.5,
219 75.2, 75.6, 83.5, 84.5, 125.6, 125.8, 128.6, 129.0, 129.6, 130.0, 133.8, 134.0, 134.2, 135.4,
220 149.8, 150.0 ppm. The diastereoselectivity of the compound was determined from ¹H NMR
221 (82:18). MS (ESI): *m/z* = 292 [M + Na]⁺; Anal. Calcd. (%) for C₁₀H₁₁N₃O₆
222 : C 44.61, H 4.21, N 15.61; Found (%): C 44.55, H 4.20, N 15.64.

223 **3(3-Nitrophenyl)-2,4-dinitrobutane (1r):** 92% yield; brown gum, IR (KBr): 2932, 1562, 1551,
224 1392 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 1.44 (d, *J* = 6.8 Hz, 3 H), 1.63 (d, *J* = 6.8 Hz, 3 H),
225 4.14- 4.23 (m, 1H), 4.77- 5.04 (m, 3 H), 7.54- 7.60 (m, 2 H), 8.10- 8.21 (m, 1 H), ppm; ¹³C NMR
226 (100 MHz, CDCl₃): δ = 17.0, 17.7, 46.9, 47.1, 75.7, 76.0, 83.9, 122.9, 123.1, 124.1, 130.5, 130.7,
227 134.2, 134.4, 135.9, 136.2, 148.5, 148.7 ppm. The diastereoselectivity of the compound was

determined from ^1H NMR (58:42). MS (ESI): $m/z = 292$ $[\text{M} + \text{Na}]^+$; Anal. Calcd. (%) for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_6$: C 44.61, H 4.21, N 15.61; Found (%): C 44.58, H 4.22, N 15.66.

3(4-Nitrophenyl)-2,4-dinitrobutane (1s): 90% yield; brown gum, IR (KBr): 2935, 1559, 1544, 1389 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): $\delta = 1.45$ (d, $J = 6.8$ Hz, 3 H), 1.64 (d, $J = 6.8$ Hz, 3 H), 4.16-4.21 (m, 1 H), 4.75 (dd, $J = 13.6, 9.2$ Hz, 1 H), 4.87-5.05 (m, 3 H), 7.41-7.48 (m, 2 H), 8.20-8.26 (m, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): $\delta = 17.0, 17.7, 46.99, 47.1, 75.7, 76.0, 83.8, 124.3, 124.6, 129.3, 141.1, 141.3, 148.1$ ppm. The diastereoselectivity of the compound was determined from ^1H NMR (76:24). MS (ESI): $m/z = 292$ $[\text{M} + \text{Na}]^+$; Anal. Calcd. (%) for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_6$: C 44.61, H 4.21, N 15.61; Found (%): C 44.66, H 4.22, N 15.57

3(4-Methoxyphenyl)-2,4-dinitrobutane (1t):³¹ 81% yield; brown gum, IR (KBr): 2970, 1551, 1540, 1373 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): $\delta = 1.39$ (d, $J = 6.8$ Hz, 3 H), 1.54 (d, $J = 6.8$ Hz, 3 H), 3.76 (s, 3 H), 3.90-3.97 (m, 1 H), 4.59 (dd, $J = 13.2, 8.0$ Hz, 1 H), 4.72-4.94 (m, 3 H), 6.83 (m, 2H), 7.05 (m, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): $\delta = 16.7, 17.8, 46.7, 47.1, 55.2, 55.5, 76.3, 77.4, 84.2, 84.7, 114.6, 114.8, 129.1, 129.5, 130.5, 131.2, 159.9$ ppm. The product was analyzed to determine the diastereoselectivity of the reaction. The diastereoselectivity (64:36 d.r.) of the reaction were determined by HPLC analysis using a CHIRALPAK AD-H column, hexane/2-propanol 36:4, flow rate 0.4 mL/min, UV 210 nm, major diastereomer: 42.51 min; minor diastereomer: 34.2, 38.2 min. MS (ESI): $m/z = 255$ $[\text{M} + \text{H}]^+$; Anal. Calcd. (%) for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_5$: C 51.97, H 5.55, N 11.02; Found (%): C 51.88, H 5.54, N 11.07.

3(4-Methylphenyl)-2,4-dinitrobutane (1u):³² 78% yield; brown gum, IR (KBr): 2936, 1565, 1553, 1378 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): $\delta = 1.41$ (d, $J = 6.4$ Hz, 3 H), 1.56 (d, $J = 6.4$ Hz, 3 H), 2.32 (s, 3 H), 3.96-3.98 (m, 1 H), 4.61 (dd, $J = 12.8, 4.8$ Hz, 1 H), 4.74-4.93 (m, 3 H), 7.02-

250 7.08 (m, 2 H), 7.14-7.18 (m, 2 H) ppm; ^{13}C NMR (100MHz, CDCl_3): δ = 16.7, 17.9, 47.0, 47.5,
251 76.2, 76.9, 84.0, 84.7, 127.8, 130.0, 130.2, 130.6, 139.0. The product was analyzed to determine
252 the diastereoselectivity of the reaction. The diastereoselectivity (60:40 d.r.) of the reaction were
253 determined by HPLC analysis using a CHIRALPAK AS column, hexane/2-propanol 95:5, flow
254 rate 1.0 mL/min, UV 210 nm, major diastereomer: 24.7, 30.7 min; minor diastereomer: 17.3,
255 18.2 min. MS (ESI): m/z = 239 $[\text{M}+\text{H}]^+$; Anal. Calcd. (%) for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4$: C 55.46, H 5.92, N
256 11.76; Found (%): C 55.40, H 5.93, N 11.80.

257 **3(1-Naphthyl)-2,4-dinitrobutane (1v):**³² 80% yield; brown gum, IR (KBr): 2939, 1567, 1550,
258 1383 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 1.39 (d, J = 5.2 Hz, 3 H), 1.57 (d, J = 6.4 Hz, 3 H),
259 4.98 (d, J = 6.4 Hz, 2 H), 5.13-5.19 (m, 2 H), 7.31 (d, J = 7.2 Hz, 1 H), 7.42-7.49 (m, 1 H), 7.54
260 (t, J = 7.2 Hz, 1 H), 7.63 (t, J = 8.0 Hz, 1 H), 7.84 (d, J = 8.0 Hz, 1 H), 7.89 (d, J = 8.4 Hz, 1 H),
261 8.17 (d, J = 7.2 Hz, 1 H) ppm; ^{13}C NMR (100MHz, CDCl_3): δ = 14.1, 15.6, 40.8, 74.9, 83.6,
262 121.8, 122.1, 125.2, 125.3, 126.4, 127.5, 129.4, 129.7, 129.9, 134.2. The product was analyzed
263 to determine the diastereoselectivity of the reaction. The diastereoselectivity (70:30 d.r.) of the
264 reaction were determined by HPLC analysis using a CHIRALPAK AD-H column, hexane/2-
265 propanol 36:4, flow rate 0.4 mL/min, UV 254 nm, major diastereomer: 29.4, 31.5 min; minor
266 diastereomer: 25.2, 27.0 min. MS (ESI): m/z = 297 $[\text{M}+\text{Na}]$; Anal. Calcd. (%) for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4$: C
267 61.31, H 5.14, N 10.21; Found (%): C 61.43, H 5.13, N 10.17.

268 **Ethyl-2-cyano-3-(3-nitrophenyl)-4-nitrobutanoate (2):** 91% yield, yellow oil, IR (KBr): 3469,
269 2988, 2255, 1740, 1558, 1480, 1023 cm^{-1} , ^1H NMR (400MHz, CDCl_3): δ 1.20 (t, J = 7.2 Hz, 3
270 H), 1.25 (t, J = 7.6 Hz, 3 H), 4.17 – 4.28 (m, 2 H), 4.34 – 4.43 (m, 1 H), 4.83 - 4.93 (m, 1 H),
271 4.97 - 5.10 (m, 2 H), 7.62 (t, J = 7.6 Hz, 1 H), 7.71-7.76 (m, 1 H), 8.21 - 8.26 (m, 2 H) ppm. ^{13}C
272 NMR (100MHz, CDCl_3): δ 13.8, 41.1, 42.1, 42.4, 63.9, 64.1, 75.3, 75.6, 113.7, 113.8, 122.8,

123.5, 124.3, 124.4, 130.8, 130.7, 134.0, 133.8, 135.6, 148.5, 148.6, 163.2, 163.4 ppm. MS
(ESI): $m/z = 308 [M+H]^+$.

Procedure for the gram scale preparation of 1,3-Dinitro-2(3-nitrophenyl)propane (1f) A mixture of 1-Nitro-3-(2-nitrovinyl)benzene (1.94 g, 10 mmol), nitromethane (1.22 g, 20 mmol) and phosphate buffer solution (pH 7.0, 20.0 mL) was vigorously stirred at 60 °C till the reaction was complete (2 h). The reaction mixture was extracted with ethyl acetate (3×100 mL). The solvent of the combined organic phases was dried with anhydrous sodium sulfate, evaporated under reduced pressure, and the resulting reaction crude was purified by column chromatography (ethyl acetate/hexane 15:85) to obtain the pure product 2.29 g (90% yield) as a white solid.

Results and discussion

To start with, a mixture of β -nitrostyrene (1 mmol) and nitromethane (5 mmol) in phosphate buffer solution (2 mL) was vigorously stirred at room temperature. After 36 h, complete conversion of the starting β -nitrostyrene to the corresponding 1,3-dinitro compound was observed and the product was isolated in 88% yield. When the reaction temperature was increased to 60 °C, the reaction gave the optimum yield within 3 h (Table 1). It is evident from the Table 1 that changes in temperature led to either increase in reaction time (Entry 2) or decrease in isolated yield (Entry 4). The fact that the reaction is catalyzed by phosphate anions in the buffer, the volume of the buffer solution was also optimized and 2 mL phosphate buffer against 1 mmol of nitroolefin was found to be optimum. Since the pH of water is also neutral, the pilot reaction was carried out in water at 60 °C as well, but the reaction did not proceed even after 12 h of vigorous stirring.

Table 1

Having optimized the reaction parameters, the substrate scope of our protocol was studied for the synthesis of various 1,3-dinitroalkenes (Chart 1). From the isolated yields, it can be concluded the protocol works well for the entire range of nitroalkenes under investigation. It can be seen from the Chart 1, that the addition of nitromethane to ring substituted β -nitrostyrenes hardly depends upon the nature of the substituents on the phenyl ring. Even the 1,3-dinitropropanes bearing aliphatic chains (entry **1l**) were formed in good yield with equal efficiency. In order to see the efficiency of our method on a gram scale, we carried out the reaction of (*E*)-1-Nitro-3-(2-nitrovinyl)benzene with nitromethane under the optimized conditions to observe that the reaction was complete within 2 h to give 90% isolated yield.

Chart 1

In an attempt to study the compatibility of our reaction conditions against compounds containing sensitive functional groups such as nitrile and ester, we carried out the Michael type addition of ethyl cyanoacetate to (*E*)-2 (3-nitrophenyl)-1-nitroethene (Figure 1) to observe that these groups were highly compatible even at 80 °C and provided excellent yields of their corresponding Michael adducts.

Figure 1: Studies on compatibility of the ester and nitrile group

As the reaction of β -nitrostyrene with nitroethane should give a diastereomeric mixture, we carried out chiral HPLC analysis in order to see if any diastereoselectivity exists for those products (entries **1m -1u**). It may be noted that our efforts to separate the diastereomeric mixture employing reverse phase C-18 column using acetonitrile-water mixture at various concentrations

failed as we observed only one peak in all the cases. When the reaction was carried out at 60 °C, no diastereoselectivity was observed by HPLC upon employing chiralcel OD-H and AD-H columns. When the reaction of β -nitrostyrene with nitroethane was carried out at room temperature, the corresponding Michael addition product was formed with good diastereoselectivity upon stirring for 60 h (Chart 2). Extension of the protocol revealed that most of the products formed have diastereoselective preferences. Mention may be made for *p*-fluoro- β -nitrostyrene (dr 97:3) and *p*-chloro- β -nitrostyrene (dr 89:11) which might be influenced by H-bond between the substituents with the reaction medium. From single crystal XRD data (CCDC 1559819) of the compound **1p** (Figure 2), it was confirmed that *anti*-product was formed predominantly over *syn*. It may be noted that in the absence of any stereoinducting factors such as sterically hindered reactants and reagents, we have achieved significant diastereoselective ratio (no enantioselective excess) in some cases due to participation of water in the six-membered transition state to yield the *anti* diastereomer in preference to the *syn*.

Figure 2. Ortep diagram of single crystal of compound **1p**

Chart 2

This preferential *anti*-selectivity might be explained by formation of the bicyclic transition states **TS1** and **TS2** with water as the third participant (Figure 3). Since **TS1** has no butane gauche- and 1,3-diaxial interactions while **TS2** has two butane gauche- and one 1,3-diaxial interactions, the formation of *anti*-Michael product might have been favored in comparison to the *syn*.

Figure 3. Probable explanation for *anti*-selectivity**Conclusion**

For the first time the nitroalkane addition to nitroalkene is reported in the presence of phosphate buffer at neutral pH without employing traditional organic and inorganic bases. The commonly encountered oligomerization products under basic reaction conditions were successfully avoided under neutral pH. Simple operational procedure, short reaction time, excellent yields are some of the highlights of our reaction protocol.

Acknowledgements: Authors acknowledge the support UGC-CAS programme of the Department of Chemistry, North Eastern Hill University (NEHU), Shillong. The analytical support from Sophisticated Analytical Instrumentation Facility, NEHU is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:.....

References

- (1) Clarke, P. A.; Santos, S.; Martin, W. H. C.; *Green. Chem.* **2007**, *9*, 438-440.
- (2) Clarke, P. A.; Zaytzev, A. V.; Whitwood, A. C.; *Tetrahedron Lett.* **2007**, *48*, 5209-5212.
- (3) Bhuyan, D.; Sarma, R.; Dommaraju, Y.; Prajapati, D.; *Green Chem.* **2014**, *16*, 1158-1162.
- (4) Xiang, H.; Chen, Y.; He, Q.; Xie, Y.; Yang, C.; *RSC Adv.* **2013**, *3*, 5807.

- 365 (5) Kalita, S. J.; Mecadon, H.; Deka, D. C.; *Tetrahedron Lett.* **2015**, 56, 731-734.
- 366 (6) Escribano, F. C.; Alcantara, M. D.; Gomez-Sanchez, A.; *Tetrahedron Lett.* **1988**, 29, 6001-
367 6004.
- 368 (7) Alcantara, M. D.; Escribano, F. C.; Gomez-Sanchez, A.; Dianez, M. J.; Estrada, M. D.;
369 Lopez-Castro, A.; Perez-Garrido, S.; *Synthesis* **1996**, 64-70.
- 370 (8) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; *Synthesis* **2004**, 1938-1914.
- 371 (9) Ballini, R.; In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed, Elsevier:
372 Amsterdam, **1997**; Vol. 19, p 117.
- 373 (10) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kessler, M.; Stuermer, R.; Zelinski, T.;
374 *Angew. Chem. Int. Ed.* 2004, 43, 788-824.
- 375 (11) Turner, N.; Carr, J. R.; in: *Biocatalysis in the Pharmaceutical and Biotechnology Industries*
376 (Ed.: R. N. Patel), CRS Press, Boca Raton, **2007**, p. 743.
- 377 (12) Pagoria, P. F.; Lee, G. S.; Mitchell, A. R.; Schmidt, R. D.; *Thermochim. Acta* **2002**, 384,
378 187-189.
- 379 (13) Ballini, R.; Barboni, L.; Fiorini, D.; Giarlo, G.; Palmieri, A.; *Green Chem.* **2005**, 7, 828-
380 829.
- 381 (14) Reyes, E.; Jiang, H.; Milelli, A.; Elsner, P.; Hazell, R. G.; Jørgensen, K. A.; *Angew. Chem.*
382 *Int. Ed.* **2007**, 46, 9202-9205.
- 383 (15) Barboni, L.; Gabrielli, S.; Palmieri, A.; Femoni, C.; Ballini, R.; *Chem. Eur. J.* **2009**, 15,
384 7867-7870.
- 385 (16) Ballini, R.; Barboni, L.; Fiorini, D.; Giarlo, G.; Palmieri, A.; *Chem. Commun.* **2005**, 2633-
386 2634.

- 387 (17) Ballini, R.; Barboni, L.; Femoni, C.; Giarlo, G.; Palmieri, A.; *Tetrahedron Lett.* **2006**, 47,
388 2295-2297.
- 389 (18) Park, D. Y.; Lee, K. Y.; Kim, J. N.; *Tetrahedron Lett.* **2007**, 48, 1633-1636.
- 390 (19) Ballini, R.; Barboni, L.; Giarlo, G.; Palmieri, A.; *Synlett* **2006**, 1956-1958.
- 391 (20) Rabalakos, C.; Wulff, W. D.; *Synlett* **2008**, 2826-2830.
- 392 (21) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M.; *Chem. Rev.* **2005**, 105, 933-
393 972.
- 394 (22) Escribano, F. C.; Alcántara, M. D.; Gómez-Sánchez, A.; *Tetrahedron Lett.* **1988**, 29, 6001-
395 6004.
- 396 (23) Baron, M.; Métay, E.; Lemaire, M.; Popowycz, F.; *J. Org. Chem.* **2012**, 77, 3598-3603.
- 397 (24) Bora, P. P.; Bez, G.; *Eur. J. Org. Chem.* **2013**, 2922-2929.
- 398 (25) Gomori, G. *Preparation of buffers for use in enzyme studies* in *Methods in Enzymology*;
399 Colowick, S. P. and Kaplan, N. O., Ed.; Academic Press Inc., New York, **1955**, Vol 1, 138-
400 146.
- 401 (26) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; *Synthesis* **2004**, 12, 1938-1940.
- 402 (27) Cwik, A.; Fuchs, A.; Hell, Z.; Clacens, J. M.; *Tetrahedron* **2005**, 61, 4015-4021.
- 403 (28) Fierro, A.; Rezende, M. C.; Boza, S. S.; Parada, M. R.; Cassels, B. K.; *J. Chem. Res.(S)*,
404 **2001**, 294-295.
- 405 (29) Roy, S. J. S.; Mukherjee, S.; *Chem. Commun.* **2014**, 50, 121-123.
- 406 (30) Ballini, R.; Barboni, L.; Fiorini, D.; Giarlo, G.; Palmieri, A.; *Green Chem.* **2005**, 7, 828-
407 829.
- 408 (31) Yang, X.; Zhou, X.; Lin, L.; Chang, L.; Liu, X.; Feng, X.; *Angew. Chem. Int. Ed.* **2008**, 47,
409 7079-7081.

- 410 (32) Dong, X. Q.; Teng, H. L.; Wang, C. J.; *Org. Lett.* **2009**, *11*, 1265-1268.
- 411 (33) Yang, W.; Du, D. M.; *Chem. Commun*, **2011**, *47*, 12706-12708.

Draft

Table 1: Effect of temperature.^a

Entry	Reaction conditions	%Yield ^b
1	Room temperature, 36 h	88
2	40 °C, 16 h	85
3	60 °C, 3 h	90
4	80 °C, 2.5 h	75

^aGeneral reaction conditions: Phosphate buffer (0.5 mL), β -nitrostyrene (0.25 mmol), nitroalkane (1.00 mmol);

^bIsolated yields

Chart 1: Synthesis of 1,3-dinitropropanes via Scheme 1.^{a, b} ^aGeneral reaction conditions: Phosphate buffer (0.5 mL), β -nitrostyrene (0.25 mmol), nitroalkane (1.25 mmol); 60^{°C}; ^bIsolated yields.

Chart 2: Diastereoselective synthesis of 1,3-dinitropropanes.^{a,b}

^aGeneral reaction conditions: room temperature, phosphate buffer (0.5 mL), β -nitrostyrene (0.25 mmol), nitroethane (1.25 mmol); ^bIsolated yields.

Scheme 1. Synthesis of 1,3-dinitro compounds

Figure 1: Studies on compatibility of the ester and nitrile group

Figure 2. Ortep diagram of single crystal of compound **1p**

Figure 3. Probable explanation for *anti*-selectivity.