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

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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 architechture.[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 profile[6-8] 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 carbacycles[12-14] and bicycle[3.31]nonanes,[15] highly substituted arenes[16-18] 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] DBU[22] 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 undergoe 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 ^{1}H NMR, ^{13}C NMR spectroscopy. ^{1}H 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 buffer**[25]

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 ^{o}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}; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.0, 77.0, 127.6, 129.3,
112 129.7, 134.5 MS (ESI): m/z = 233 $[M + Na]^{+}$; Anal. Calcd. (%) for $C_9H_{10}N_2O_4$: C 51.43, H 4.80,
113 N 13.33; Found (%): C 51.37, H 4.79, N 13.38.

1,3-Dinitro-2(4-fluorophenyl)propane (1b): 90% yield; yellow solid; m.p. 84-86 ^{o}C, IR (KBr): 2917, 1553, 1495, 1429, 1372 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.28- 4.35 (quintet, *J* = 7.2 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;^{13}C NMR (100 MHz, $CDCl_3$): 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 = 247 Hz), ppm; MS (ESI): m/z = 252 $[M + Na]^+$; Anal. Calcd. (%) for $C_9H_9FN_2O_4$: C 47.37, H 3.98, N 12.28; Found (%): C 47.31, H 3.97, N 12.32.

1,3-Dinitro-2(4-chlorophenyl)propane (1c):[27] 82% yield; Yellow solid; mp 77-79 ^{o}C; IR (KBr): 2924, 1563, 1559, 1384, 825 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27-4.34 (quintet, *J* = 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; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1, 76.5, 128.7, 129.8, 132.6, 135.2 ppm; MS (ESI): m/z = 267 $[^{35}M + Na]^+$, 269 $[^{37}M + Na]^+$; Anal. Calcd. (%) for $C_9H_9ClN_2O_4$: C 44.19, H 3.71, N 11.45; Found (%): C 44.11, H 3.69, N 11.50.

1,3-Dinitro-2(4-bromophenyl)propane (1d):[28] 78% yield; colourless liquid; IR (KBr): 2924, 1561, 1548, 1386, 1373 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.19-4.26 (m, 1 H), δ 4.63-4.74 (m, 4 H), δ 7.04 (d, *J* =8.4 Hz, 2 H), δ 7.44 (d, *J* =8.4 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.8, 75.7, 126.1, 128.5, 130.1, 134.1 ppm; MS (ESI): m/z = 311 $[^{79}M + Na]^+$, 313 $[^{81}M + Na]^+$; Anal. Calcd. (%) for $C_9H_9FN_2O_4$: C 37.39, H 3.14, N 9.69; Found (%): C 37.44, H 3.13, N 9.74.

1,3-Dinitro-2(2-nitrophenyl)propane (1e): 90% yield; brown gum; IR (KBr): 2924, 1561, 1549, 1429, 1377 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.44- 4.51 (quintet, *J* = 7.2 Hz, 1H), 4.80- 4.90 (m, 4H), 7.57-7.67 (m, 2H), 8.15- 8.21 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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. Calcd. (%) for $C_9H_9N_3O_6$: 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, $CDCl_3$): 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; ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_9H_9N_3O_6$: 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 ^oC; IR (KBr): 2923, 1563, 1551, 1380, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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; ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{10}H_{12}N_2O_4$: 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, $CDCl_3$): 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; ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{10}H_{12}N_2O_5$: 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, $CDCl_3$): 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; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1, 55.3, 76.9, 114.9, 128.5, 159.9 ppm; MS (ESI): m/z = 241 $[M+H]^+$; Anal. Calcd. (%) for $C_{10}H_{12}N_2O_5$: C 50.00, H 5.04, N 11.66; Found (%): C 50.10, H 5.05, N 11.73.

1,3-Dinitro-2(3,4-methylenedioxyphenyl)propane (1j):[29] 77% yield; brown gum; IR (KBr): 2920, 1563, 1548, 1443, 1393, 1249, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ =4.19 (quintet, J = 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 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.5, 76.8, 101.6, 107.5, 107.5, 109.1, 121.0, 127.4, 148.0, 148.5; MS (ESI): m/z = 277 $[M+Na]^+$; Anal. Calcd. (%) for $C_{10}H_{10}N_2O_6$: C 47.25, H 3.97, N 11.02; Found (%): C 47.11, H 3.99, N 11.11.

1,3-Dinitro-2(1-naphthyl)propane (1k):[29] 82% yield; brown gum; IR (KBr): 2923, 1567, 1551, 1390, 1371, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.88-4.98 (m, 4 H), 5.23-5.30 (m, 1 H), 7.32 (d, J = 7.6 Hz, 1 H), 7.44 (t, *J* = 8 Hz, 1 H), 7.56 (t, *J* = 7.2Hz, 1 H), 7.64 (m, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 7.91 (d, J = 8.0 Hz,1 H), 8.18 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 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; MS (ESI): m/z = 283 $[M+Na]^+$; Anal. Calcd. (%) for $C_{10}H_{12}N_2O_5$: C 60.00, H 4.65, N 10.76; Found (%): C 59.77, H 4.66, N 10.79.

1,3-Dinitro-2(2-furyl)propane (1l):[29] 85% yield; yellow gum; IR (KBr): 2930, 1555, 1543, 1378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.44 (q, *J* = 6.4 Hz, 1 H), 4.80 (d, *J* = 6.4 Hz, 4 H), 6.27 (d, *J* = 2.8 Hz, 1H), 6.34 (d, *J* = 1.6 Hz, 1H), 7.39 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.8, 74.5, 108.9, 110.8, 143.4, 147.0 ppm. MS (ESI): m/z = 223 $[M+Na]^+$; Anal. Calcd. (%) for $C_7H_8N_2O_5$: C 42.01, H 4.03, N 14.00; Found (%): C 42.18, H 4.02, N 14.06.

1-Nitro-2-(nitromethyl)pentane (1m):[26] 80% yield; yellow gum; IR (KBr): 2920, 1561, 1550, 1393 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.8 Hz, 3 H), 1.38-1.46 (m, 4 H), 2.87 (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; ^{13}C NMR (100 MHz, $CDCl_3$): 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 ^oC. 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.

3(4-Chlorophenyl)-2,4-dinitrobutane (1p):[33] 82% yield; yellow solid; IR (KBr): 2930, 1563, 1556, 1390, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 7.6 Hz, 3 H), 1.56 (d, *J* = 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 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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 was analyzed to determine the diastereoselectivity of the reaction. The diastereoselectivity (89:11 d.r.) of the reaction were determined by HPLC analysis using a CHIRALPAK AS column, hexane/2-propanol 95:5, flow rate 1.0 mL/min, UV 210 nm, major diastereomer: 41.5, 48.0 min; minor diastereomer: 32.3, 48.0 min. MS (ESI): m/z = 281 $[M + Na]^+$; Anal. Calcd. (%) for $C_{10}H_{11}ClN_2O_4$: C 46.43, H 4.29, N 10.83; Found (%): C 46.49, H 4.28, N 10.87.

3(2-Nitrophenyl)-2,4-dinitrobutane (1q):[31] 89% yield; brown gum, IR (KBr): 2933, 1565, 1549, 1393 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.60 (d, J = 6.8Hz, 3 H), 1.71 (d, *J* = 6.8 Hz, 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), 7.53-7.65 (m, 2 H), 7.96 (d, J = 8.0 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1, 18.1, 41.5, 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, 149.8, 150.0 ppm. The diastereoselectivity of the compound was determined from ^1H NMR (82:18). MS (ESI): m/z= 292 $[M + Na]^+$; Anal. Calcd. (%) for $C_{10}H_{11}N_3O_6$: C 44.61, H 4.21, N 15.61; Found (%): C 44.55, H 4.20, N 15.64.

3(3-Nitrophenyl)-2,4-dinitrobutane (1r): 92% yield; brown gum, IR (KBr): 2932, 1562, 1551, 1392 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.8 Hz, 3 H), 1.63 (d, *J* = 6.8 Hz, 3 H), 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; ^{13}C NMR (100 MHz, $CDCl_3$): 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, 134.2, 134.4, 135.9, 136.2, 148.5, 148.7 ppm. The diastereoselectivity of the compound was

determined from ^{1}H NMR (58:42). MS (ESI): m/z = 292 $[M + Na]^{+}$; Anal. Calcd. (%) for $C_{10}H_{11}N_3O_6$: 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}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 ^{1}H NMR (76:24). MS (ESI): m/z = 292 $[M+Na]^{+}$; Anal. Calcd. (%) for $C_{10}H_{11}N_3O_6$: 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}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $[M+H]^{+}$; Anal. Calcd. (%) for $C_{11}H_{14}N_2O_5$: 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}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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-

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, 76.2, 76.9, 84.0, 84.7, 127.8, 130.0, 130.2, 130.6, 139.0. The product was analyzed to determine the diastereoselectivity of the reaction. The diastereoselectivity (60:40 d.r.) of the reaction were determined by HPLC analysis using a CHIRALPAK AS column, hexane/2-propanol 95:5, flow rate 1.0 mL/min, UV 210 nm, major diastereomer: 24.7, 30.7 min; minor diastereomer: 17.3, 18.2 min. MS (ESI): m/z = 239 $[M+H]^+$; Anal. Calcd. (%) for $C_{11}H_{14}N_2O_4$: C 55.46, H 5.92, N 11.76; Found (%): C 55.40, H 5.93, N 11.80.

3(1-Naphthyl)-2,4-dinitrobutane (1v):[32] 80% yield; brown gum, IR (KBr): 2939, 1567, 1550, 1383 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, J = 5.2 Hz, 3 H), 1.57 (d, *J* = 6.4 Hz, 3 H), 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 (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), 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, 121.8, 122.1, 125.2, 125.3, 126.4, 127.5, 129.4, 129.7, 129.9, 134.2. The product was analyzed to determine the diastereoselectivity of the reaction. The diastereoselectivity (70:30 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 254 nm, major diastereomer: 29.4, 31.5 min; minor diastereomer: 25.2, 27.0 min. MS (ESI): m/z = 297 [M+Na]; Anal. Calcd. (%) for $C_{14}H_{14}N_2O_4$: C 61.31, H 5.14, N 10.21; Found (%): C 61.43, H 5.13, N 10.17.

Ethyl-2-cyano-3-(3-nitrophenyl)-4-nitrobutanoate (2): 91% yield, yellow oil, IR (KBr): 3469, 2988, 2255, 1740, 1558, 1480, 1023 cm^{-1}, ^{1}H NMR (400MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.2 Hz, 3 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), 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 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 ^oC 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 ^oC, 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 ^oC 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 ^{o}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 ^{o}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.

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Supplementary data

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

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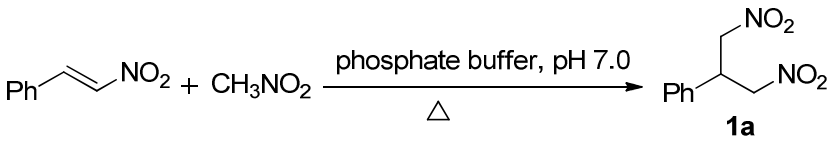
Table 1: Effect of temperature.[a]

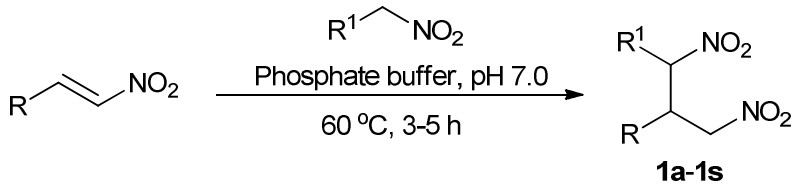


Entry	Reaction conditions	%Yield[b]
1	Room temperature, 36 h	88
2	40 °C, 16 h	85
3	60 °C, 3 h	90
4	80 °C, 2.5 h	75

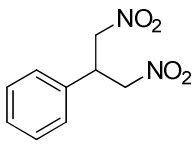
[a]General reaction conditions: Phosphate buffer (0.5 mL), *β*-nitrostyrene (0.25 mmol), nitroalkane (1.00 mmol);

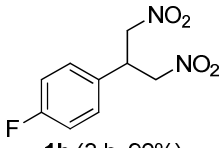
[b]Isolated yields

Chart 1: Synthesis of 1,3-dinitropropanes via Scheme 1.[a, b]



1a-1s


1a (3 h, 90%)



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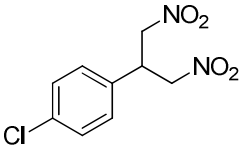
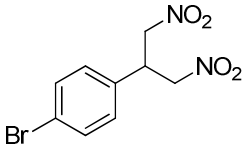
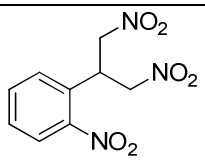


1c (3.5 h, 82%)



1d (3.5 h, 78%)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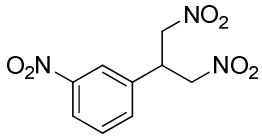
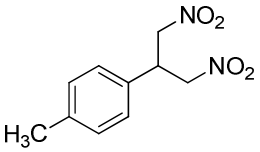


1f (2 h, 93%)



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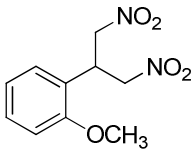

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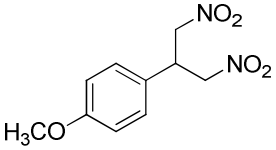

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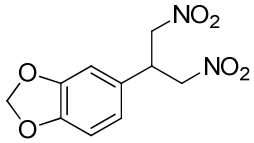
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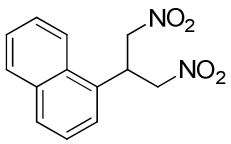
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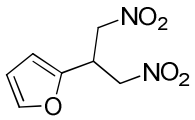
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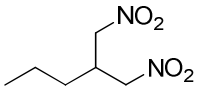
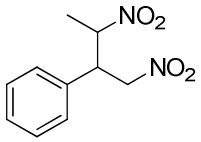

1m (3.5 h, 80%)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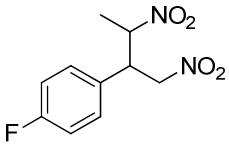
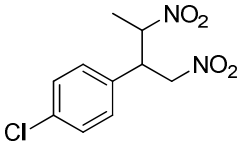
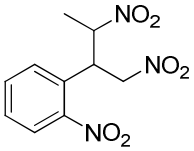


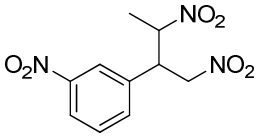
1o (5h, 80%)



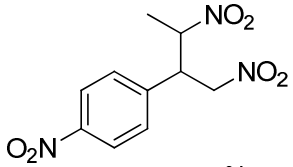
1p (5h, 82%)



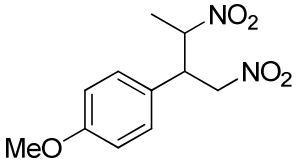
1q (3.5h, 89%)



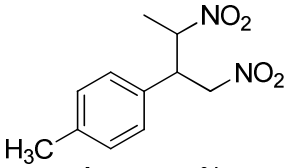
1r (3.5h, 92%)



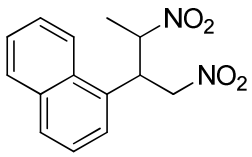
1s (3.5h, 90%)



1t (5.5h, 81%)

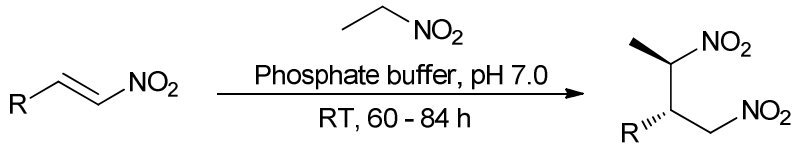


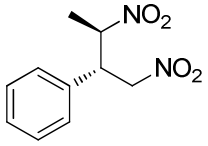
1u (5h, 78%)


1v (5h, 80%)

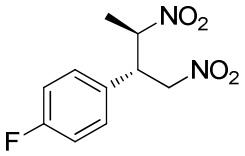
[a]General reaction conditions: Phosphate buffer (0.5 mL), *β*-nitrostyrene (0.25 mmol), nitroalkane (1.25 mmol); 60 °C; [b]Isolated yields.

Chart 2: Diastereoselective synthesis of 1,3-dinitropropanes.[a,b]

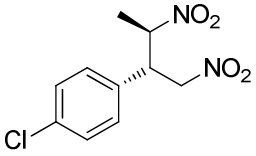




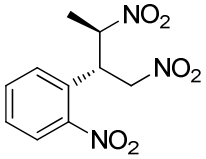
1n
(60h, 70:30 dr, 85%)



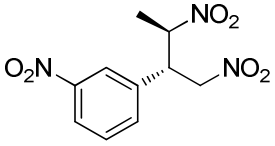
1o
(72 h, 97:3 dr, 85%)



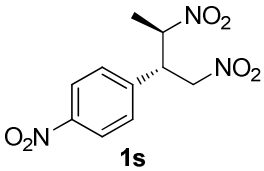
1p
(72 h, 89:11 dr, 80%)



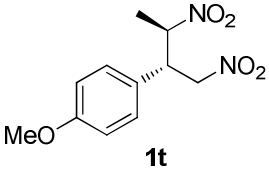
1q
(60 h, 82:18 dr,91%)



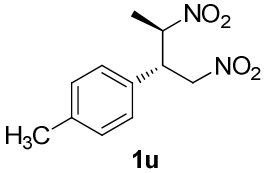
1r
(60 h, 56:44 dr, 90%)



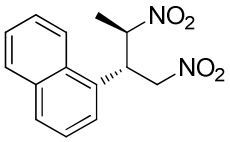
1s
(60 h, 76:24 dr, 94%)



1t
(84 h, 64:36 dr, 80%)

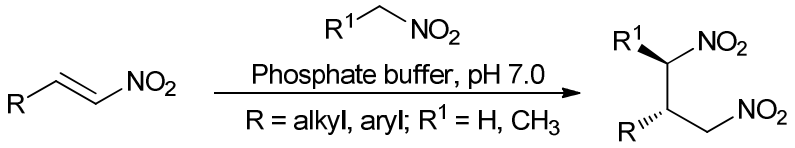


1u
(60 h, 60:40 dr, 73%)



1v
(84 h, 70:30 dr, 75%)

[a]General reaction conditions: room temperature, phosphate buffer (0.5 mL), *β*-nitrostyrene (0.25 mmol), nitroethane (1.25 mmol); [b]Isolated yields.



Scheme 1. Synthesis of 1,3-dinitro compounds

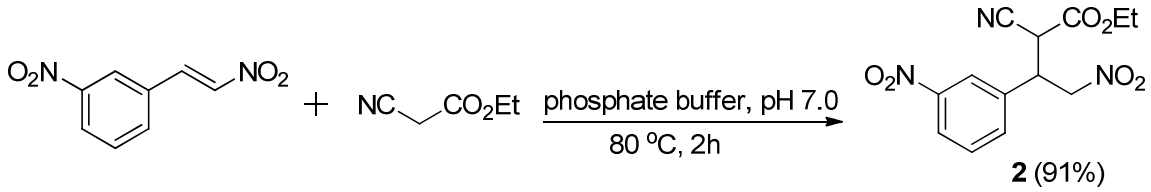


Figure 1: Studies on compatibility of the ester and nitrile group

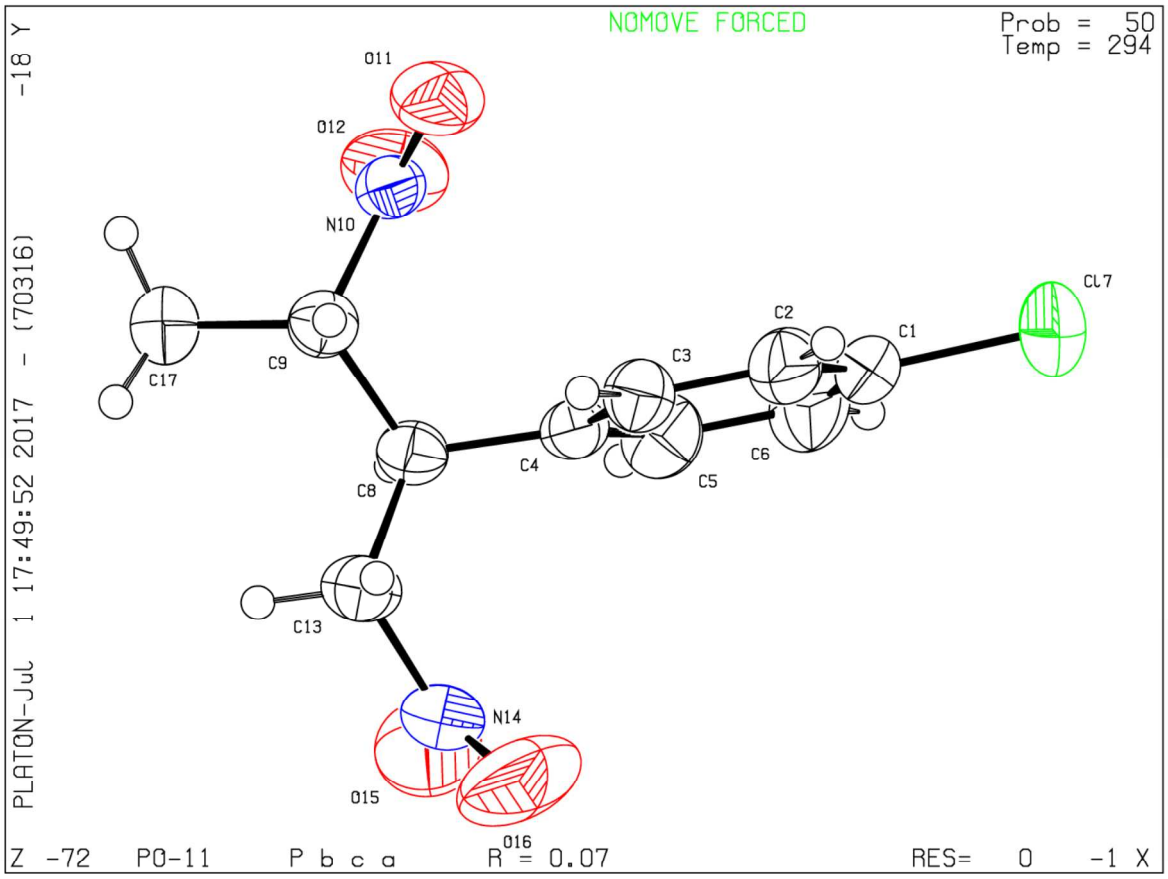


Figure 2. Ortep diagram of single crystal of compound **1p**

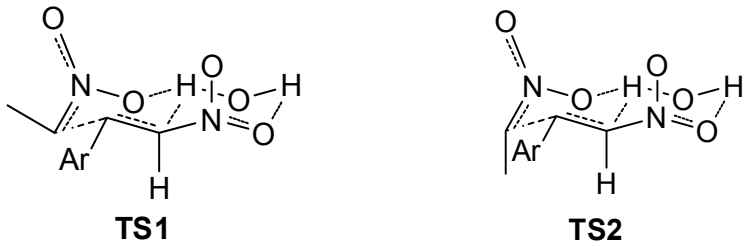


Figure 3. Probable explanation for *anti*-selectivity.