Nitroalkanes as Alkyl Anion Synthons – A New Approach to the Synthesis of 2-Substituted *N*-Ethyl Succinimides and 2-Substituted Succinate Diesters via Nitroalkanes

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2-Substituted *N*-ethyl succinimide and 2-substituted succinate diesters were obtained by two key steps: (i) Michael addition of a nitroalkane to the appropriate enedione derivative under basic conditions (DBU), with the concomitant elimination of nitrous acid, and (ii) selective reduction of the obtained enone with nickel boride, in methanol/THF. In this context the nitroalkane acts as an alkyl anion synthon. By this method trimethyl tricarboxylates were also synthesized.

The use of nitro compounds as reactive intermediates in organic synthesis has attracted the interest of many researches in recent years[1–9]. Both the activating effect of the nitro group, and its facile transformation into various functional groups have extended the importance of nitro compounds in the synthesis of complex molecules. Furthermore, the discovery of new reactions that cause the displacement of the nitro group by hydrogen has opened new pathways in organic synthesis, since the nitro group can be removed after it has fulfilled its activating role for the reaction in which carbon-carbon bonds are formed[10].

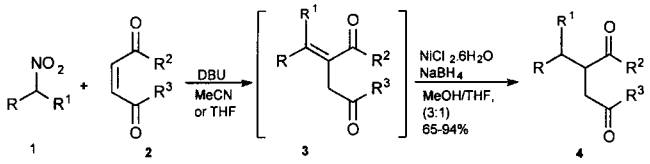
In this context, the usefulness of employing functionalized nitroalkanes as reagents for functionalized alkyl anion synthons via two key step reactions: i.e. the C–C bond-forming reaction followed by replacement of the nitro group by hydrogen, has been reviewed[11]. However, the most widely used methods have a number of ecological disadvantages for widespread industrial use. This applies particularly to the frequently used organotin compounds[10].

The discovery[12] of the formation of unsaturated carbonyl derivatives by Michael addition of nitroalkanes to enediones, via elimination of nitrous acid, suggested a new strategy to employ nitroalkanes as alkyl anion synthons.

To test this idea we chose to develop a new synthesis of 2-substituted *N*-ethyl succinimides **4a–c** and 2-substituted succinate diesters **4d–l**. The compounds **4a–g** are important intermediates in many synthetic transformations[13–15], with the ω-hydroxyester **4g** being of particular interest since this kind of compound is the immediate precursor of macrolactones[16]. Moreover, the tricarboxylate methyl esters **4h–l** are of great value as building blocks for many synthetic transformations[17–23] and as molecules that show important biological activity[24].

Our sequence involves firstly the Michael addition of the appropriate nitroalkane **1** to the enedione derivative (*N*-ethylmaleimide and dimethyl maleate) **2** (Scheme 1) in acetonitrile and with DBU as base, then selective reduction of the crude enone **3**, obtained, through elimination of nitrous acid, to afford the title compound **4**.

Scheme 1



4	R	R1	R2	R3
a	CH_3	CH_3	–N(Et)–	
b	$(CH_3)_2CHCH_2$	H	–N(Et)–	
c	$MeO_2C[CH_2]_3$	H	–N(Et)–	
d	CH_3CH_2	H	OCH_3	OCH_3
e	$CH_3[CH_2]_2$	H	OCH_3	OCH_3
f	CH_3	CH_3	OCH_3	OCH_3
g	$HO[CH_2]_{11}$	H	OCH_3	OCH_3
h	$CH_3O_2C[CH_2]_2$	H	OCH_3	OCH_3
i	$CH_3O_2C[CH_2]_3$	H	OCH_3	OCH_3
j	$CH_3O_2C[CH_2]_4$	H	OCH_3	OCH_3
k	$CH_3O_2C[CH_2]_5$	H	OCH_3	OCH_3
l	$CH_3O_2C[CH_2]_{13}$	H	OCH_3	OCH_3

After several attempts to achieve the best reaction conditions for an efficient selective reduction of **3**, we found that nickel boride[25] converted **3** into **4** in excellent yields. The boride is easily prepared by the reduction of a Ni(II) salt with sodium borohydride in methanol/THF. Nickel boride also catalyzes the hydrogenation of olefins and acetylenes[26], and acts as a reducing agent toward a variety of functional groups. Although its detailed structure is unknown, its elemental composition is consistent with the formula Ni_2B, and this species contains hydrogen that is gradually released[27]. Thus, as reported in Table 1, the compounds **4** were obtained in good to excellent yields.

In conclusion, the present methodology represents a new chemoselective and alternative procedure for the synthesis of the title compounds. Additionally, this new way of employing the nitroalkanes **1** as alkyl anion synthons could stimulate their use as a source of carbanions. We believe

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Table 1. Selected physical and spectroscopic data of 2-substituted-1,4-dione derivatives **4**

Product 4	Yield (%)	mp [°C]	IR ν [cm^{-1}]	^{1}H NMR δ, J [Hz]
a	65	oil	1690	0.85 (d, *J* = 6.8, 3 H, *CH*$_3$-CH), 1.0 (d, *J* = 6.9, 3 H, *CH*$_3$-CH), 1.18 (t, *J* = 7.2, 3 H, *CH*$_3$-CH$_2$), 2.25–2.37 (m, 1 H, *CH*(CH$_3$)$_2$), 2.42 (dd, *J* = 4.6 and 16, 1 H, *H*-CHCO), 2.58–3.73 (m, 2 H, CHCO and HC*H*-CO), 3.55 (d, *J* = 7.2, 2 H, *CH*$_2$CH$_3$)
b	68	oil	1680	0.88 (dd, *J* = 1.5 and 6.6, 6 H, *(CH*$_3$*)*$_2$CH), 1.1–1.6 (m, 7 H), 2.35 (dd, *J* = 4.3 and 16, 1 H, *H*CHCO), 2.65–2.87 (m, 2 H, CHCO and HC*H*CO), 3.5 (q, *J* = 7.0, 2 H, *CH*$_2$CH$_3$)
c	90	oil	1720 1680	1.13 (t, *J* = 7.2, 2 H, *CH*$_3$CH$_2$), 1.22–2.0 (m, 6 H, 3 CH$_2$), 2.25–2.42 (m, 3 H, *CH*$_2$COOMe and *H*CHCO), 2.7–2.9 (m, 2 H, CHCO and HC*H*CO), 3.53 (q, *J* = 7.2, 2 H, *CH*$_2$CH$_3$), 3.67 (s, 3 H, OCH$_3$)
d	92	oil	1720	0.88 (t, *J* = 7.2, 3 H, CH$_3$), 1.2–1.68 (m, 4 H, CH$_2$CH$_2$), 2.43 (dd, *J* = 4.7 and 16, 1 H, *H*CHCO), 2.65–2.9 (m, 2 H, CHCO and HC*H*CO), 3.67 (s, 3 H, OCH$_3$), 3.69 (s, 3 H, OCH$_3$)
e	90	oil	1720	0.87 (t, *J* = 7.2, 3 H, CH$_3$), 1.19–1.69 (m, 8 H, 4 CH$_2$), 2.43 (dd, *J* = 4.6 and 15.9, 1 H, *H*CHCO), 2.66–2.9 (m, 2 H, *CH*CO and HC*H*CO), 3.67 (s, 3 H, COCH$_3$), 3.69 (s, 3 H, OCH$_3$)
f	94	oil	1730	0.92 (dd, *J* = 3.0 and 6.9, 6 H, (CH$_3$)$_2$), 1.88–2.05 (m, 1 H, CH), 2.43 (dd, *J* = 5.5 and 16, 1 H, *H*CHCO,), 2.68–2.78 (m, 2 H, CHO and HC*H*CO), 3.68 (s, 3 H, OCH$_3$), 3.7 (s, 3 H, OCH$_3$)
g	68	oil	3400 1720	1.2–1.6 (m, 22 H, 11 CH$_2$), 2.43 (dd, *J* = 4.6 and 15.9, 1 H, *H*CHO), 2.63–2.9 (m, 2 H, CHO and HC*H*CO), 3.63 (t, *J* = 7.0, 2 H, *CH*$_2$OH), 3.67 (s, 3 H, OCH$_3$), 3.7 (s, 3 H, OCH$_3$)
h	70	oil	1720	1.5–1.7 (m, 4 H, CH$_2$CH$_2$), 2.53 (m, 2 H, CH$_2$CO), 2.44 (dd, *J* = 4.7 and 15.9, 1 H, *H*CHCO), 2.63–2.9 (m, 2 H, CHCO and HC*H*CO), 3 .67 (s, 3 H, OCH$_3$), 3.68 (s, 3 H, OCH$_3$), 3.7 (s, 3 H, OCH$_3$)
i	72	oil	1720	1.2–1.75 (m, 6 H, 3 CH$_2$), 1.3 (t, *J* = 7.3, 2 H, CH$_2$CO), 2.42 (dd, *J* = 4.8 and 15.9, 1 H, *H*CHCO), 2.63–2.92 (m, 2 H, CHCO and HC*H*CO), 3.66 (s, 3 H, OCH$_3$), 3.67 (s, 3 H, OCH$_3$)
j	80	oil	1725	1.2–1.7 (m, 8 H, 4 CH$_2$), 2.3 (t, *J* = 7.1, 2 H, CH$_2$CO), 2.43 (dd, *J* = 4.6 and 16, 1 H, *H*CHCO), 2.65–2.9 (m, 2 H, CHCO and HC*H*CO), 3.66 (s, 3 H, OCH$_3$), 3.67 (s, 3 H, OCH$_3$), 3.7 (s, 3 H, OCH$_3$)
k	73	oil	1720	1.2–1.7 (m, 10 H, 5 CH$_2$), 2.3 (t, *J* = 7.2, 2 H, CH$_2$CO), 2.42 (dd, *J* = 4.6 and 16, 1 H, *H*CHCO), 2.63–2.9 (m, 2 H, CHCO and HC*H*CO), 3.67 (s, 3 H, OCH$_3$), 3.68 (s, 3 H, OCH$_3$), 3.71 (s, 3 H, OCH$_3$)
l	86	45–47	1720	1.15–1.7 (m, 26 H, 13 CH$_2$), 2.3 (t, *J* = 7.2, 2 H, CH$_2$CO), 2.43 (dd, *J* = 4.7 and 16.1, 1 H, *H*CHCO), 2.65–2.9 (m, 2 H, CHCO and HC*H*CO), 3.68 (s, 3 H, OCH$_3$), 3.69 (s, 3 H, OCH$_3$), 3.71 (s, 3 H, OCH$_3$)

Table 2. Microanalyses of 2-substituted-1,4-dione derivatives **4**

	Molecular formula calcd. (Molecular mass found)	C	H	N
4a	$C_9H_{15}NO_2$	63.88	8.93	8.27
	(169.22)	63.69	9.02	8.38
4b	$C_{11}H_{19}NO_2$	66.97	9.70	7.09
	(197.28)	67.11	9.78	6.98
4c	$C_{12}H_{19}NO_4$	59.73	7.93	5.80
	(241.28)	59.92	7.78	5.64
4d	$C_9H_{16}O_4$	57.43	8.56	
	(188.22)	57.60	8.70	
4e	$C_{11}H_{20}O_4$	61.09	9.32	
	(216.28)	60.98	9.46	
4f	$C_9H_{16}O_4$	57.43	8.56	
	(188.22)	57.64	8.44	
4g	$C_{18}H_{34}O_5$	65.42	10.37	
	(330.46)	65.33	10.50	
4h	$C_{11}H_{18}O_6$	53.65	7.36	
	(246.11)	53.44	7.46	
4i	$C_{12}H_{20}O_6$	56.37	7.74	
	(260.28)	56.51	7.60	
4j	$C_{13}H_{22}O_6$	56.92	8.08	
	(274.31)	57.04	7.98	
4k	$C_{14}H_{24}O_6$	58.31	8.39	
	(288.34)	58.48	8.24	
4l	$C_{22}H_{40}O_6$	65.97	10.06	
	(400.56)	66.12	9.94	

that this methodology has some merits over that using organometallic reagents.

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Experimental

The reactions were monitored by TLC and/or GC analyses, performed on a Carlo Erba Fractorap 4160 using a capillary column of duran glass (0.32 mm × 25 m), stationary phase OV1 (film thickness 0.4–0.45 nm). – ^{1}H NMR: Varian Gemini 200, in $CDCl_3$ at 200 MHz, with tetramethylsilane as internal standard. – IR: Perkin-Elmer 257. The nitroalkanes **1** were commercially available (Aldrich) or prepared, in good yields, as previously reported[1,28].

The compounds **4** were purified by flash chromatography[29] on Merck silica gel (0.040–0.063 mm). The microanalysis data are presented in Table 2.

Alkylation of Enediones (**2**) *to 2-Substituted 1,4-Diones* (**4**). – *General Procedure:* To a solution of nitroalkane **1** (5 mmol) and enedione derivative **2** (5 mmol) in MeCN (20 ml) or THF (20 ml, when *N*-ethyl maleimide was used as acceptor), DBU (0.76 g, 5 mmol) was added at room temp. After stirring for 0.5–3 h (TLC or GC), the solution was diluted with Et_2O (70 ml) and washed with 2 N HCl (3 × 10 ml). The organic layer was dried ($MgSO_4$) and evaporated affording the crude enone **3** which was used for the following reduction without purification.

The compound **3** and $NiCl_2 \cdot 6\ H_2O$ (8.3 g, 35 mmol) were dissolved in 100 ml of methanol/THF (3:1) in a magnetically stirred flask at 0°C. Sodium borohydride (4 g, 105 mmol) was added in small portions. The mixture was stirred for an additional 1–4 h (TLC or GC). The solution was then filtered through Celite and washed with methanol/THF. The filtrate was evaporated to yield the crude **4**, which was then purified by flash chromatography.

[1] D. Seebach, E. W. Colvin, F. Lehr, T. Weller, *Chimia* **1979**, *33*, 1–18.
[2] A. G. M. Barrett, G. G. Graboski, *Chem. Rev.* **1986**, *86*, 751–762.
[3] G. W. Kabalka, R. S. Varma, *Org. Prep. Proced. Int.* **1987**, *19*, 283–328.
[4] R. H. Fischer, H. M. Weitz, *Synthesis* **1980**, 261–282.
[5] G. Rosini, R. Ballini, M. Petrini, E. Marotta, P. Righi, *Org. Prep. Proced. Int.* **1990**, *22*, 707–746.
[6] R. Tamura, A. Kamimura, N. Ono, *Synthesis* **1991**, 423–434.
[7] H. Stach, M. Hesse, *Tetrahedron* **1988**, *44*, 1573–1590.
[8] H. Feuer, A. T. Nielsen, *Nitro Compounds*, VCH, Cambridge, **1990**.
[9] V. V. Perekalin, E. S. Lipina, V. M. Berestovitskaya, D. A. Efremov in *Nitroalkenes*; Wiley: Chichester, **1994**.
[10] N. Ono, A. Kaji, *Synthesis* **1986**, 693–704.
[11] G. Rosini, R. Ballini, *Synthesis* **1988**, 833–847.
[12] [12a] M. C. Kloetzel, *J. Am. Chem. Soc.* **1948**, *70*, 3571–3576. – [12b] W. Rudiger, W. Klose, *Tetrahedron Lett.* **1967**, 1177–1178. – [12c] R. Ballini, G. Bosica, *Tetrahedron* **1995**, *51*, 4213–4222.
[13] J. Fuhrhop, G. Penzlin in *Organic Synthesis*, VCH, Weinheim, **1986**.
[14] E. J. Corey, X. M. Cheng in *The Logic of Chemical Synthesis*, Wiley, New York, **1989**.

[15] T. L. Ho in *Tactics of Organic Synthesis*, Wiley, New York, **1994**.
[16] [16a] T. G. Back, *Tetrahedron* **1977**, *33*, 3041–3059. – [16b] H. Yamada, S. Ohsawa, T. Sugai, H. Ohta, S. Yoshikawa, *Chem. Lett.* **1989**, 1775–1776. – [16c] H. Kuno, M. Shibagaki, K. Takahashi, I. Honda, H. Matsushita, *Chem. Lett.* **1992**, 571–574.
[17] S. Dutt, A. Banerjee, *Indian J. Chem. Sec. B* **1976**, *14B*, 489–493.
[18] Okamura Oil Mill, Ltd. Jpn Kokai Tokkyo Koho 80139366, **1980**; *Chem. Abstr.* **1981**, *94*, 120895.
[19] H. J. Albrecht, V. Hartmann, W. Scheel, F. Schilling, *DVS Ber* **1990**, *129*, 101–105; *Chem. Abstr.* **1991**, *115*, 140597.
[20] M. Paker, U. S. Patent 4758366, **1988**; *Chem. Abstr.* **1988**, *109*, 192724.
[21] J. W. Huffman, R. Sawdaye, *Synth. Commun.* **1981**, *11*, 979–981.
[22] W. Liao, R. F. Christman, J. D. Johnson, D. S. Millington, J. R. Hass, *Environ SCI Technol* **1982**, *16*, 403–410; *Chem. Abstr.* **1982**, *97*, 11438.
[23] Y. Yarim-Agaer, M. Plavsic, P. J. Flory, *Polym. Prep.* **1984**, *24*, 233–234; *Chem. Abstr.* **1984**, *101*, 7846.
[24] E. Lohaus, I. Blos, R. Karl, W. Ruediger, W. Schaefer, *Naturwissenschaften* **1982**, *69*, 89–90.
[25] For a review, see: B. Ganem, J. O. Osby, *Chem. Rev.* **1986**, *86*, 763–780.
[26] C. A. Brown, V. K. Ahuja, *J. Org. Chem.* **1973**, *38*, 2226–2230.
[27] P. C. Maybury, R. W. Mitchell, M. F. Hawthorne, *J. Chem. Soc., Chem. Commun.* **1974**, 534–535.
[28] R. Ballini, M. Petrini, V. Polzonetti, *Synthesis* **1992**, 355–357.
[29] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

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