Ethyl 2-nitroacetoacetate as a new synthetic equivalent of ethoxycarbonylnitrile oxide

V. P. Kislyi, A. L. Laikhter, B. I. Ugrak, and V. V. Semenov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328

It was shown that ethyl 2-nitroacetoacetate is a synthetic precursor of ethoxycarbonylnitrile oxide as well as of isoxazole- and isoxazoline-3-carboxylic acids and their esters. The elimination of acetic acid from ethyl 2-nitroacetoacetate occurs in a mixture of acetic acid and acetic anhydride in the presence of strong mineral acids, *e.g.*, H_2SO_4, at room temperature and gives isoxazolines in yields of up to 85—91 %.

Key words: ethoxycarbonylnitrile oxide, isoxazoles, isoxazolines.

The efficient procedure for the nitration of carbonyl compounds in a two-phase system[1] makes it possible to obtain functional derivatives of α-nitroketones in considerable amounts. One of the main directions of the decomposition of these nitroketones in acid media is the formation of nitrile oxides,[2] which serve as intermediates in the syntheses of isoxazoles, oxadiazoles, and heterocycles of other types.

$$CH_3COCH_2{-}X \xrightarrow{NO_2^+} CH_3COCH(NO_2){-}X \xrightarrow[-CH_3COOH]{} X{-}C{\equiv}N{\rightarrow}O$$

Ethoxycarbonylnitrile oxide (ECNO) (**1**) and its adducts with alkenes (**2**) or alkynes (**3**), *i.e.*, isoxazolines (**4**) or isoxazoles (**5**), are useful synthetic intermediates, in particular, in the syntheses of γ-hydroxy-α-amino acids[3—5] and α-ketocarboxylic acids or their oximes.[6] Furthermore, several isoxazoline-3-carboxylic acids are of special interest as physiologically active compounds.[7] In a review (Ref. 8), ECNO was called "an underestimated synthon in organic chemistry".

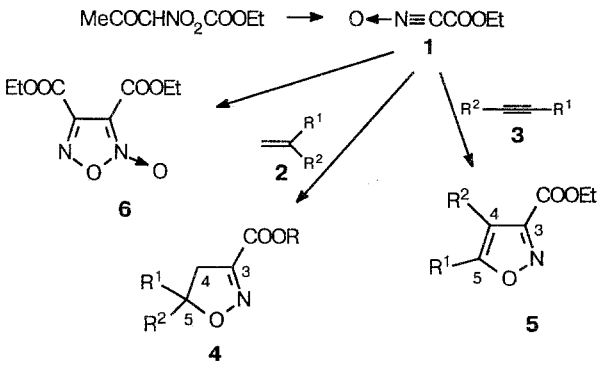
The following methods for generating ECNO are known: in basic media from the respective chloroxime[9] or nitroacetic ester[10] and with acid catalysis from nitroacetic ester[11] or nitromalonic ester.[12] However, there remains interest in the elaboration of procedures for synthesizing isoxazolines and in finding new sources of ECNO based on available raw materials.[12]

Previously,[13] the transformation of ethyl 2-nitroacetoacetate (ENA) under mild conditions (AcOH, 1 h, ~20 °C) to bis(ethoxycarbonyl)furoxane **6** was reported. The formation of ECNO as the intermediate was postulated, but adducts with alkenes were not obtained.

The unusually mild conditions of this reaction and the availability of ENA[13] prompted us to study the possibility of using ENA as a new synthetic analog of ECNO. For example, decomposition of ENA in the presence of alkenes **2a—g** or alkynes **3a—c** resulted in the respective isoxazolines **4a—g** or isoxazoles **5a—c** (Scheme 1, Table 1).

These reactions with alkenes containing electron-withdrawing substituents normally proceed with very high yields. However, the reactions with alkenes containing electron-donating substituents require greater amounts of catalysts and/or longer reaction times, while the yields of the products are much lower. For example, the yield of compound **4f** is as low as 30 %, and the

Scheme 1



4a—f, 5a—c: R = Et; **4g**: R = H; **2a, 4a**: R^1 = EtOOC, R^2 = H; **2b, 4b**: R^1 = NC, R^2 = H; **2c, 4c**: R^1 = EtOOC, R^2 = Me; **2d, 4d**: R^1 = $MeCOOCH_2$, R^2 = H; **2e, 4e**: R^1 = $BrCH_2$, R^2 = H; **2f, 4f**: R^1 = $Me(CH_2)_3$, R^2 = H; **2g, 4g**: R^1 = Ph, R^2 = H; **3a, 5a**: R^1 = H, R^2 = H; **3b, 5b**: R^1 = MeOOC, R^2 = MeOOC; **3c, 5c**: R^1 = H, R^2 = $CF_3(OCF_2CF_2)_2OCF_2$

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 103—105, January, 1994.

1066-5285/94/4301-98 $12.50

Table 1. Yields of cycloaddition products

Compound	Alkene ENA ratio	τ/h[a]	Amount of H_2SO_4 (mol. %)	B.p./°C (p/Torr) [M.p./°C]	Yield[b] (%)
4a	1.1	3	30	100—105(0.1)	91
4b	1.1	3	15	80(0.1)	85
4c	1.05	3	30	110(0.1)	63
4d	1.2	8	45	100(0.05)	70
4e	1.3	8	30	[52—54]	85
4f	2.0	72	45	80(0.07)	18
4g[c]				[108—109]	12
5a	8	30		45—50(0.5)	70
5b	1.1	3	30	120(0.5)	82
5c	1.5	48	30	110(0.5)	45[d]

[a] τ is the reaction time. [b] The yields are given with respect to the isolated product. [c] See Experimental. [d] Yield according to GLC-MS data.

synthesis of compound **4g** must be performed by a modified procedure involving the preparation of a sodium salt of ENA. Such alkenes as *tert*-butyl vinyl ether, 2-methoxypropene, or vinyl acetate do not undergo this reaction at all but rather undergo resinification under these conditions. Some alkenes (cyclohexene, ethyl β,β-dimethylacrylate, tri- and tetrachloroethylene, butyndiol diacetate) do not form adducts but are stable under the reaction conditions due to their known low activity in the 1,3-dipolar cycloaddition.

The conditions required for generating ECNO from ENA are much milder than those for the acid-catalyzed generation of ECNO from other precursors.[11,12] It should be noted that the reaction with alkenes is regiospecific and gives only 5-substituted isoxazolines, whereas the reaction with perfluoro-2,5,8-trioxanon-1-ylacetylene (**3c**) results in mixtures of 4- and 5-substituted isoxazoles (in a ratio of 10 : 1, respectively, according to GLC-MS data).

Unlike the method for synthesizing isoxazoles from ECNO under alkaline conditions, where the reaction with electron-deficient alkenes occurs in low yields,[12] the method proposed by us makes it possible to synthesize isoxazoles with electron-withdrawing substituents more efficiently.

The structures of the compounds obtained were confirmed by ^1H and ^{13}C NMR spectral data (Tables 2 and 3).

Experimental

^1H NMR spectra were obtained on a Bruker WM-250 spectrometer (250.13 MHz). ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument (75.47 MHz). ENA and its sodium salt were prepared by the known procedures.[1] All of the unsaturated compounds were distilled just before use.

General procedure for the decomposition of ENA (for all isoxazolines 4a—g, 5a—c, except 4g and furoxane 6). ENA (3.5 g, 2.95 mL, 0.02 mol) was added to an AcOH—Ac_2O (5 : 1) mixture (10 mL) containing an alkene (0.02—0.04 mol, see Table 1), and then a catalytic amount of H_2SO_4 was added. The mixture was stirred and left to stand at 20 °C. After the reaction was completed, the mixture was poured into water and extracted with chloroform. The chloroform extract was washed with water and dried with Na_2SO_4. Chloroform was evaporated, and the residue was distilled.

Bis(ethoxycarbonyl)furoxane (6). ENA (3.5 g, 2.95 mL, 0.02 mol) was added to an AcOH—Ac_2O (5 : 1) mixture

Table 2. ^1H NMR chemical shifts and coupling constants

Compound	δ (J/Hz)					
	3-COOEt		H^a(C-4)	H^b(C-4)	H(C-5)	Other signals
	CH_3	OCH_2				
4a	1.23 t (7.1)	4.17 q (7.1)	3.39 dd (17.5, 9.3)	3.40 dd (17.5, 10.2)	5.12 dd (9.3, 10.2)	5-COOEt: 1.28 t (7.1, Me); 4.26 q (7.1, CH_2)
4b	1.26 t (7.2)	4.25 q	3.47 dd (18.0, 6.8)	3.57 dd (18.0, 11.3)	5.38 dd (6.8, 11.3)	—
4c	1.25 t (7.0)	4.20 q (7.1)	3.03 d (17.5)	3.65 d (17.5)	—	1.61 s (5-Me); 5-COOEt: 1.31 t (7.0, Me) 4.29 q (7.0, OCH_2)
4d	1.29 t (7.2)	4.41 q (7.2)	2.98 dd (17.8, 7.9)	3.25dd (17.8, 9.5)	4.96 dddd (7.9, 9.5, 3.9, 5.6)	2.01 s ($OOCCH_3$); CH_2OOC: 4.08 dd (12.1, 3.9); 4.19 dd (12.1, 5.6)
4e	1.38 t (7.2)	4.37 q (7.2)	3.38 dd (18.0, 7.5)	3.20 dd (18.0, 11.0)	5.07 dddd (7.5, 11.0, 4.5, 7.5)	CH_2Br: 3.43 dd (11.0, 4.5); 3.55 dd (11.0, 7.5)
4f	1.37 t (7.2)	4.32 q (7.2)	2.82 dd (17.5, 8.6)	3.22 dd (17.5, 10.9)	4.77 dddd (8.6, 10.9, 6.3, 7.2)	$CH_3CH_2CH_2CH_2$: 0.9 m, 1.4 m, 1.6—1.8 m
4g			3.25 dd (17.8, 9.1)	3.66 dd (17.8, 11.6)	5.87 dd (9.1, 11.6)	7.30—7.45 m (Ph); 5.30 br.s (COOH)
5a	1.38 t (7.2)		4.41 q (7.2)	6.75 d (1.8)	8.52 d (1.8)	—
5b	1.32 t (7.1)		4.38 q (7.1)	—	—	3.87 s (4-MeOOC) 3.92 s (5-MeOOC)
6	1.42 t (7.1)		4.51 q (7.1)	—	—	4-EtOOC: 1.28 t (7.1, Me), 4.26 q (7.1, CH_2)

Table 3. ^{13}C NMR chemical shifts and coupling constants

Compound	δ ($J_{^{13}C,^1H}$/Hz)						
	C-3	C-4	C-5	3-COO	Me(OEt)	CH_2(OEt)	Other atoms
4a	150.96 td (7.1, 2.7)	37.37 td (139.7, 2.3)	79.69 dt (157.5, 2.6)	159.66 t (3.2)	13.86 qt (127.4, 2.0)	62.09 tq (151.3, 4.5)	Me(5-Et): 13.86 qt (127.4, 2.0); CH_2(5-Et): 62.00 tq (151.3, 4.5); 5-COO: 168.71 ttd (2.5, 3.5, 2.5)
4b	151.47 td (7.0, 2.8)	39.52 td (142.0, 3.3)	68.06 dt (166.6, 2.0)	158.59 t (3.3) (127.6, 2.6)	13.58 qt (141.1, 4.5)	62.41 tq	CN: 116.09 dt (3.8, 9.0)
4c	150.94 t (6.9)	43.25 tq (138.6, 4.3)	88.44 qt (7.0, 3.0)	160.04 t (3.2)	13.80 qt (127.5, 2.6)	62.12 tq (148.5, 4.4)	Me(5-Et): 13.95 tq (127.2, 2.1); CH_2(5-Et): 62.2 tq (150.3, 4.4); 5-COO: 170.59 qddd (3.0, 2.5, 6.3, 2.7); 5-Me: 23.28 qdd (130.0, 4.5, 6.7)
4d	151.26 td (7.1, 1.7)	35.54 t (137.3)	80.52 dt (154.8, 2.5)	160.15 t (3.4)	13.91 qt (130.5, 2.6)	61.96 qt (148.5, 4.4)	Me: 20.49 q (130.0); CH_2O: 64.16 tt (148.5, 8.0); COO: 170.39 tq (2.9, 6.8)
4e	151.29 td (7.0, 2.0)	38.30 td (130.0, 3.5)	81.70 dt (156.4, 2.7)	160.35 t (3.2) (127.5, 2.6)	14.12 qt (148.6, 4.5)	62.29 tq	CH_2Br: 32.51 ttd (153.0, 8.5, 1.7)
4f	150.89 td (7.0, 2.0)	40.68 td (132.0, 3.0)	86.29 dt (158.0, 2.5)	162.55 c	—	—	Ph: 126.01, 129.02, 129.1, 139.11
4g	151.37 td (7.4, 2.4)	38.41 ddt (135.2, 138.5, 4.0)	84.17 dm (151.3)	160.95 t (3.4)	14.12 qt (130.1, 2.6)	61.91 tq (148.3, 4.5)	Bu: 13.89, 22.42, 27.22, 34.75
5a	155.64 dd (6.4, 4.0)	105.18 dd (187.4, 14.0)	156.0 dd (204.8, 11.0)	159.76 t (3.3) (127.5, 2.7)	14.06 qt (148.7, 4.5)	62.19 tq	^{17}O: 168.1 (ON); 356.4 (COO)
5b	154.26 s	117.57 s	158.64 s	157.70 t (3.2)	13.75 qt (127.6, 2.8)	62.91 tq (149.3, 4.5)	4-CH_3: 53.23 q (148.4); 4-COO: 155.39 q (4.0); 5-CH_3: 53.43 q (149.2); 5-COO: 159.97 q (4.0)
6	149.72 t (0.9)	107.70 t (1.0)	4-COO: 157.48 t (3.4) 5-COO: 155.74 t (3.3)		Me(4-Et): 14.12 qt (127.4, 2.6) Me(5-Et): 14.13 qt (127.4, 2.6)	CH_2(4-Et): 64.22 tq (149.0, 4.5) CH_2(5-Et): 66.08 tq (151.2, 4.5)	^{15}N: −1.0 (N), −15.7 (N-O); ^{14}N: −15.7 (N-O)

(10 mL) containing H_2SO_4 (0.5 mL), and the mixture was stirred for 1 h. The mixture was poured into water and extracted with chloroform. The extract was washed with water and dried with Na_2SO_4. Chloroform was evaporated, and the residue was distilled. B.p. 160 °C (12 Torr). Yield 86 %.

5-Phenylisoxazoline-3-carboxylic acid (4g). The sodium salt of ENA (4.14 g, 0.02 mol) was dissolved in an AcOH—Ac_2O (5 : 1) mixture (10 mL) containing styrene (0.02—0.04 mol) and H_2SO_4 (0.04 mol), and the reaction mixture was kept for 1 h at 20 °C. Then the mixture was poured into water and extracted with chloroform. The extract was washed with water and dried with Na_2SO_4. Chloroform was evaporated, and aqueous 10 % NaOH (7 mL) was added. The mixture was stirred for 3 h at 40 °C and cooled to 0 °C. 2 *N* HCl was added, and the precipitate was filtered off and recrystallized from hexane.

Ethyl (perfluoro-2,5,8-trioxanon-1-yl)isoxazole-3-carboxylate (5c) was obtained by the general procedure, but extra chloroform (10 mL) was added. MS: [M^+] 507, [M^+−F] 488, [M^+−OEt] 462.

References

1. V. P. Kislyi, A. L. Laikhter, B. I. Ugrak, and V. V. Semenov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 103 [*Russ. Chem. Bull.*, 1994, **43**, 70 (Engl. Transl.)].
2. T. Simmons and K. Kreuz, *J. Org. Chem.*, 1968, **33**, 836.
3. K. E. Harding, T. E. Marman, and Nam Do-Hyum, *Tetrahedron*, 1985, **44**, 5605.
4. G. Zimmerman, W. Hass, H. Faash, H. Schmalle, and W. A. Konig, *Lieb. Ann. Chem.*, 1985, 2165.
5. M. V. Kashutina, S. L. Ioffe, V. M. Shitkin, N. O. Cherskaya, V. A. Korenevskii, and V. A. Tartakovskii, *Zh. Org. Khim.*, 1973, **43**, 1715 [*J. Org. Chem. USSR*, 1973, **43** (Engl. Transl.)].
6. V. Jager, H. Grund, and W. Schwab, *Angew. Chem.*, 1979, **1**, 91.
7. J. Philippe, *Ger. Offen*, 2,065, 430 (25 Oct. 1973).
8. A. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410.
9. T. E. Rave and D. S. Breslow, *J. Org. Chem.*, 1971, **36**, 3813.
10. T. Shimizu, Y. Hayashi, H. Hiroshi, and K. Teramura, *Bull. Chem. Soc. Japan*, 1986, **59**, 2827.
11. T. Shimizu, Y. Hayashi, and K. Teramura, *Bull. Chem. Soc. Japan*, 1984, **57**, 2531.
12. T. Shimizu, Y. Hayashi, and K. Teramura, *Bull. Chem. Soc. Japan*, 1985, **58**, 2519.
13. S. Sifniades, *J. Org. Chem.*, 1975, **40**, 3562.

Received June 15, 1993