Synthesis of 5-Acyl-3-(ethoxycarbonyl)-2-isoxazolines 2-Oxides by a Tandem Conjugate Addition–Ring Closure of Ethyl Nitroacetate with α-Bromo Enones

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Over the past few years the utilization of 2-isoxazolines in organic synthesis has been steadily growing because of the great versatility with which these heterocyclic compounds can be converted into useful building blocks like γ-amino alcohols, β-hydroxy ketones, and β-hydroxy nitriles, acids, and esters.[1] Hence it is clear that the "isoxazoline route"[1] would be expanded if new methods, besides the well- and long-known nitrile oxide cycloaddition,[2] for the preparation of this type of heterocyclic in a functionalized form would be made available.

Some time ago we found a new approach to the stereoselective preparation of 4-hydroxylated-2-isoxazolines based on a tandem nitroaldol–ring closure of nitroacetic esters[3] with aldehydes bearing a leaving group on the α-position, in the presence of a base, followed by the deoxygenation of the intermediate 2-isoxazoline 2-oxide (Figure 1).

With 2,3-epoxy aldehydes[4] and 2-bromo aldehydes[5] as electrophiles the process proved to be an alternative and effective method for the stereoselective preparation of functionalized 2-isoxazolines.

In the course of a project devoted to the utilization of nitroalkanes in organic synthesis,[6] and in particular toward a better understanding of the scope and limits of this tandem process, we thought that α-bromo-α,β-unsaturated ketones **1** could be suitable electrophilic substrates: in this case a conjugate addition would be the first step of the process.

Indeed, in the presence of a base, ethyl nitroacetate reacts with α-bromo enones to form substituted 5-acyl-3-(ethoxycarbonyl)-2-isoxazolines 2-oxide. The first step, the conjugate addition to the enone system, unmasks the electrophilicity of the carbon bearing the bromine atom, thus allowing the second step, the ring closure, to take place and to afford the corresponding heterocyclic derivative (Figure 2).

This reaction is performed at room temperature both under heterogeneous conditions with chromatographic alumina as a base without any solvent, and under homogeneous conditions usually with triethylamine in diethyl ether.

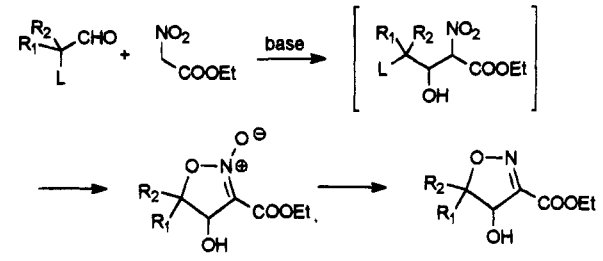


Figure 1.

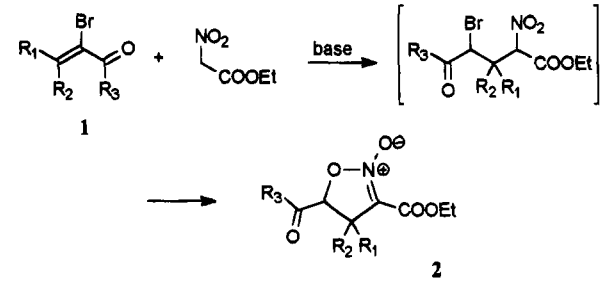


Figure 2.

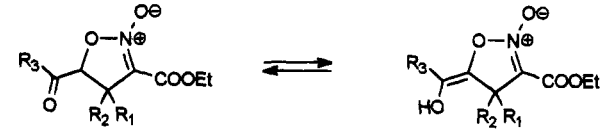


Figure 3.

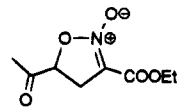
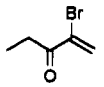
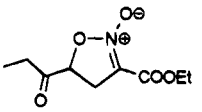
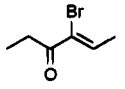
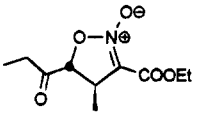
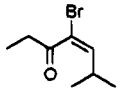
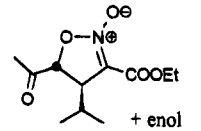
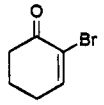
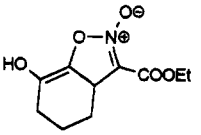
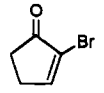
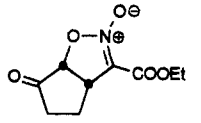
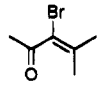
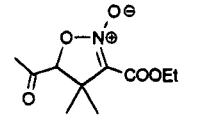
Table 1 summarizes the results obtained with several α-bromo enones, which were readily prepared from the corresponding enones.[7] Similar results are obtained under heterogeneous and homogeneous conditions, although slightly better yields are obtained under the latter conditions. The reaction rate is strongly dependent on the degree of substitution of the enone β-carbon. With unsubstituted enones (entries a, b of Table 1) the reaction is complete within 0.5 h. With monosubstituted enones (entries c–f of Table 1) completeness is reached in the range of 24–48 h, while with disubstituted substrates (entry g of Table) after 72 h only 5% of starting material was consumed. For entries a–f the reaction is much faster and equally high yielding as the corresponding nitrile oxide cycloaddition which usually takes several days or even weeks to complete. It should be noted that in the case of entries c, d the products are obtained in the keto–enol mixture; the tautomerism involves only the more acidic proton at C5 of the isoxazoline ring, and the keto form is obtained only in the less strained (4,5-trans) configuration Figure 3.[8]

The equilibrium between the two forms appears to be fast only in the presence of the base since the isolated forms are stable enough to allow a full characterization. In this regard it should be noted that the two cyclic enones behave very differently: α-bromocyclohexenone

(1) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.
(2) Padwa, A. Intermolecular 1,3-Dipolar Cycloaddtions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1069.
(3) Shipchandler, M. T. *Synthesis* **1979**, 666.
(4) (a) Rosini, G.; Galarini, R.; Marotta, E.; Righi, P. *J. Org. Chem.* **1990**, *55*, 781. (b) Rosini, G. The Henry (Nitroaldol) Reaction. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 321.
(5) Rosini, G.; Marotta, E.; Righi, P.; Seerden, J. P. *J. Org. Chem.* **1991**, *56*, 6258.
(6) For reviews, see: (a) ref 2b. (b) Rosini, G.; Ballini, R.; Petrini, M.; Marotta, E.; Righi, P. *Org. Prep. Proc. Int.* **1990**, *22*, 707. (c) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.
(7) α-Bromo enones are readily available from the corresponding enones through several well-established procedures. In our hands the one of choice was that reported by Chow, Y. L.; Bekker, B. H. *Can. J. Chem.* **1982**, *60*, 2268. For alternative procedures see: (a) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic M. R. *Tetrahedron Lett.* **1992**, *33*, 917. (b) Buckley, D. J.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2193. (c) Ley, S. V.; Whittle, A. J. *Tetrahedron Lett.* **1981**, *22*, 3301. (d) Amice, P.; Blanco, L.; Conia, J. M. *Synthesis* **1976**, 196.
(8) Relative stereochemical configuration assignments of the products were based upon *J* values obtained from the ^{1}H NMR spectra.

0022-3263/95/1960-6624$09.00/0

Table 1. Results Obtained in the Reaction of Ethyl Nitroacetate with α-Bromo Enones

Entry	Reagent	Product	Homogenous Conditions		Heterogenous conditions	
			Time (h)	Yield (%)	Time (h)	Yield (%)
a			0.25	93	0.25	70
b			0.25	95	0.40	66
c	 *E,Z* mixture	 + enol	36	99	36	92
d		 + enol	48	63	not performed	
e			24	89	40	72
f			24	92	48	70
g			72	no reaction	72	no reaction

(**1e**) gave the corresponding 5-acyl-2-isoxazoline **2e** only in the enol form, while α-bromocyclopentenone (**1f**) gave the corresponding product **2f** only in the keto form, probably due to the strain involved with the bridgehead double bond in the bicyclo[3.3.0] system.

In conclusion this work has added the 5-acyl-3-(ethoxycarbonyl)-2-isoxazoline moiety to the array of functionalized 2-isoxazolines that can be built with the tandem process between activated primary nitroalkanes which possess a potential double nucleophilicity with multicenter electrophiles such as α-bromo enones.

The reported enantioselective reduction of deoxygenated 5-acyl-2-isoxazolines by bakers' yeast makes these substrates valuable chiral building blocks,[9] now easily available.

Experimental Section

General. Melting points are uncorrected. Yields are referred to isolated pure products. Proton and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in $CDCl_3$ solvent. If not already stated, chemical shifts are expressed in ppm downfield from TMS as internal standard. Signal multiplicities were established by DEPT experiments. Flash chromatographic separations were performed using Merck Silica gel 60 (70–230 mesh ASTM). For TLC analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used.

General Procedure for the Reaction of α-Bromo Enones with Ethyl Nitroacetate under Heterogeneous Conditions. In a three-necked round-bottomed flask, equipped with a mechanical stirrer and $CaCl_2$ drying tube, the bromo ketone (10–20 mmol) and an equimolar amount of ethyl nitroacetate were mixed and cooled at 0 °C with an ice–water bath. Chromatographic alumina (Fluka, basic type, pH 9.5 ± 0.3, Brockmann grade I) was added under vigorous stirring until complete adsorption of the reactants is achieved. A slightly exothermic reaction developed for several minutes. The cooling bath was removed, and the mixture was left at rt with occasional stirring. The course of the reaction was monitored by TLC (eluant ether: petroleum ether = 7:3) and when complete the alumina is thoroughly and carefully washed on a glass filter (G3) with CH_2Cl_2. After evaporation of the solvent, the crude product was purified by flash chromatography (eluant ether:petroleum ether = 7:3). For reaction time and chemical yield of each product see Table 1.

General Procedure for the Reaction of α-Bromo Enones with Ethyl Nitroacetate in Homogeneous Conditions. In a three-necked round-bottomed flask, equipped with magnetical stirring and with a $CaCl_2$ drying tube, was placed a solution of the bromo enone (10 to 20 mmol) and an equimolar amount of ethyl nitroacetate in ether (2 mL/mmol of bromo enone). The solution was cooled at 0 °C with an ice–water cooling bath, and 1 equiv of triethylamine was added all at once. The cooling bath was removed and the course reaction was monitored by TLC (eluant ether:petroleum ether = 7:3). After the starting materials were completely consumed, the mixture was washed with

(9) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. Chem. Rev. **1992**, *92*, 1071–1140, and references cited therein.

water and then with brine. The organic phase was dried over Na_2SO_4 and evaporated at reduced pressure. The crude product was purified by flash chromatography (eluant ether:petroleum ether = 7:3). For reaction time and chemical yield of each product see Table 1.

5-Acetyl-3-(ethoxycarbonyl)-2-isoxazoline 2-Oxide (2a). After purification a pale yellow oil was obtained: IR (film) 1773, 1630, 1248 cm^{-1}; ^1H NMR δ 4.95 (dd, 1H, J = 6.2, 9.8 Hz), 4.32 (q, 2H, J = 7.2 Hz), 3.66 (dd, 1H, J = 16.8, 9.8 Hz), 3.58 (dd, 1H, J = 16.8, 6.2 Hz), 2.36 (s, 3H), 1.32 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 205.1, 158.8, 106.9, 77.5, 62.3, 33.3, 26.8, 14.5. Anal. Calcd for $C_8H_{11}NO_5$: C, 47.75; H, 5.51; N, 6.96. Found: C, 47.78; H, 5.53; N, 7.00.

3-(Ethoxycarbonyl)-5-propanoyl-2-isoxazoline 2-Oxide (2b). Flash chromatography of the crude product afforded a clear oil: IR (film) 1738, 1629, 1248 cm^{-1}; ^1H NMR δ 5.08 (dd, 1H, J = 10.4, 6.1 Hz), 4.32 (q, 2H, J = 7.2 Hz), 3.66 (dd, 1H, J = 17.2, 10.4 Hz), 3.56 (dd, 1H, J = 16.2, 6.1 Hz), 2.74 (q, 2H, J = 7.2 Hz), 1.33 (t, 3H, J = 7.2 Hz), 1.12 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 207.8, 158.9, 107.2, 77.0, 62.2, 33.1, 32.3, 14.1, 6.8. Anal. Calcd for $C_9H_{13}NO_5$: C, 50.21; H, 6.09; N, 6.51. Found: C, 50.29; H, 6.03; N, 6.48.

(4,5-*trans*)-3-(Ethoxycarbonyl)-4-methyl-3-propanoyl-2-isoxazoline 2-Oxide (2c) and Its Enol. Flash chromatography afforded the ketone and the enol as clear oils in a 8:2 ratio. Ketone: IR (film) 1729, 1623, 1233 cm^{-1}; ^1H NMR δ 5.05 (d, 1H, J = 7.5 Hz), 4.35 (q, 2H, J = 7.1 Hz), 3.90 (dq, 1H, J = 7.5, 7.2 Hz), 2.65 (q, 2H, J = 7.0 Hz), 1.35 (t, 3H, J = 7.2 Hz), 1.23 (d, 3H, J = 7.2 Hz), 1.12 (t, 3H, J = 7.0 Hz); ^{13}C NMR δ 206.2, 158.8, 112.4, 82.2, 62.4, 41.3, 34.7, 14.5, 13.4, 6.8. Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.38; H, 6.60; N, 6.11. Found: C, 52.30; H, 6.69; N, 6.14. Enol: IR (film) 3434, 1727, 1623, 1231 cm^{-1}; ^1H NMR δ 5.20 (s, 1H, disappears after D_2O exchange), 4.35 (q, 2H, J = 7.1 Hz), 3.70 (q, 1H, J = 6.0 Hz); 2.70 (m, 2H), 1.38 (t, 3H, J = 7.1 Hz), 1.32 (d, 3H, J = 6.0 Hz), 1.20 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 205.0, 160.3, 154.5, 108.2, 62.8, 46.5, 29.2, 14.4, 9.9, 8.0.

(4,5-*trans*)-5-Acetyl-3-(ethoxycarbonyl)-4-(1-methylethyl)-2-isoxazoline 2-Oxide (2d) and Its Enol. Separation afforded the ketone as a clear oil and the enol as a pale yellow oil in a 1:1 ratio. Ketone: ^1H NMR δ 4.72 (d, 1H, J = 2.8 Hz), 4.45 (q, 2H, J = 7.1 Hz), 3.68 (dd, 1H, J = 4.1, 2.8 Hz), 2.45 (m, 1H), 2.37 (s, 3H), 1.44 (t, 3H, J = 7.1 Hz), 1.05 (d, 3H, J = 6.5 Hz), 0.97 (d, 3H, J = 6.8 Hz). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.26; H, 7.01; N, 5.71. Enol: IR (film) 3433, 1727, 1629, 1227 cm^{-1}; ^1H NMR δ 5.19 (s, 1H, disappears after D_2O exchange), 4.40 (q, 2H, J = 7.2 Hz), 3.58 (d, 1H, J = 4 Hz), 2.50 (m, 1H), 2.36 (s, 3H), 1.40 (t, 3H, J = 7.2 Hz), 1.12 (d, 3H, J = 6.0 Hz), 1.04 (d, 3H, J = 6.3 Hz).

3-Aza-9-(ethoxycarbonyl)-5-hydroxy-2-oxabicyclo[4.3.0]-nona-5,8-diene 8-oxide (2e). Flash chromatography afforded a colorless solid (mp 67–68 °C). IR (KBr) 3431, 1709, 1589, 1238 cm^{-1}; ^1H NMR δ 5.25 (s, 1H, disappears after D_2O exchange), 4.40 (q, 2H, J = 7.2 Hz), 3.68 (dd, 1H, J = 5.2, 5.0 Hz), 2.68 (ddd, 1H, J = 17.2, 5.0, 4.5 Hz), 2.52 (ddd, 1H, J = 17.2, 7.8, 8.6 Hz), 1.90 (m, 4H), 1.42 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 201.7, 159.5, 154.5, 103.0, 62.1, 53.0, 35.6, 24.7, 18.5, 13.6. Anal Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.40; H, 6.62; N, 6.13.

3-Aza-3-(ethoxycarbonyl)-2-oxabicyclo[3.3.0]octan-8-one 3-Oxide (2f). Purification of the crude material afforded a colorless solid (mp 92–94 °C): IR (KBr) 1740, 1622, 1250 cm^{-1}; ^1H NMR δ 4.75 (d, 1H, J = 10.0 Hz), 4.48 (m, 3H), 2.47 (m, 4H), 1.38 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 210.1, 159.1, 109.5, 76.2, 62.8, 45.2, 35.0, 24.8, 14.8. Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.20; H, 6.12; N, 6.48.

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