

A NOVEL SYNTHESIS OF 2,3-DIHYDROOXAZOLES FROM DIMETHYL
 N-ETHOXYCARBONYLMETHYLIMINODITHIOCARBONATE AND AROMATIC ALDEHYDES

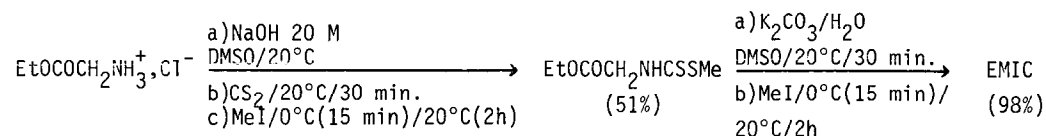
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We report the synthesis of 5-aryl-2-ethoxycarbonyl-4-methylthio-2,3-dihydrooxazoles from a cyclocondensation reaction between dimethyl N-ethoxycarbonylmethyliminodithiocarbonate and aromatic aldehydes.

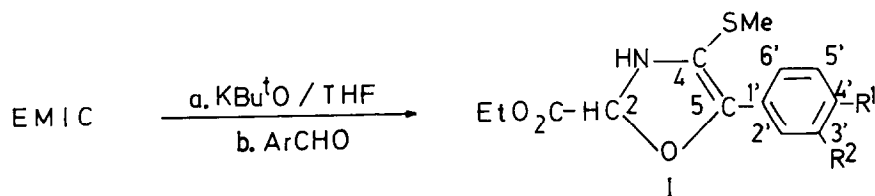
We wish to report a new chemical tool for the construction of heterocyclic ring systems. The reagent is dimethyl N-ethoxycarbonylmethyliminodithiocarbonate (EMIC). It is an easily prepared, stable and very cheap reagent.

EMIC has been prepared from glycine ethyl ester hydrochloride, carbon disulfide and methyl iodide, isolating previously the methyl N-ethoxycarbonylmethyldithiocarbamate¹.



As will be shown here and in future papers in this series, EMIC can be used to add a C=N=C unit to unsaturated systems, in particular unsaturated electrophiles C=Z (Z:O,S,N) and to obtain heterocyclic compounds.

Aromatic aldehydes, for instance, are converted efficiently in a one-pot reaction into 5-aryl-2-ethoxycarbonyl-4-methylthio-2,3-dihydrooxazoles, I.



Compound	R ¹	R ²	M.P. (°C) ²	%yield ^a
Ia	H	H	99-100	84(71)
Ib	Me	H	75-77	66(56)
Ic	MeO	H	71-72	52(52)
Id	Cl	H	98-100	96(57)
Ie	OCH ₂ O		100-102	56(51)

^aChromatographic yield (isolated product).

The reaction is most conveniently performed as follows. On a stirred suspension of 1.2 eq. of $\text{KBU}^{\text{t}}\text{O}$ in dry THF^3 (at -78°C under N_2) is added dropwise a disolution of 1 eq. of EMIC in dry THF (30 min.) and 1.5 eq. of ArCHO in dry THF ($-78^\circ\text{C}/30$ min. — $20^\circ\text{C}/2$ h.). The product is obtained upon dilution with water and is purified from a column chromatography of silicagel (petroleum ether/ethyl acetate: 95/5 (v/v) and is crystallized twice from petroleum ether. All new compounds are fully characterized by their spectra (IR, ^1H -, ^{13}C -NMR decoupled and off-resonance and SM)⁴ together with correct elemental analysis.

Ia ($\text{R}^1=\text{R}^2=\text{H}$).

IR⁵ $\nu(\text{cm}^{-1})$: 3180; 1695; 1650; 1630.

$^1\text{H-NMR}$ ⁶ $\delta(\text{ppm})$: 2.27(s, 3H, SCH_3); 6.15-7.93(m, 7H, NH, Ar, CH cycle).

$^{13}\text{C-NMR}$ ⁷ $\delta(\text{ppm})$: 12.47(c, SCH_3); 14.19(c, CH_3CH_2); 61.81(t, CH_2CH_3); 124.17(s, C5); 128.60, 129.72, 129.97(d, $\text{C}2^-$, $\text{C}3^-$, $\text{C}4^-$); 133.39(s, $\text{C}1^-$); 133.57(broad d, C2); 165.06(s, C4); 168.12(s, CO_2Et).

MS.m/e: 267(0.7); 265(8.7); 217(35.1); 172(23.0); 144(13.5); 117(100).

Ib ($\text{R}^1=\text{Me}$; $\text{R}^2=\text{H}$).

IR⁵ $\nu(\text{cm}^{-1})$: 3280; 1710; 1640; 1600.

$^1\text{H-NMR}$ ⁶ $\delta(\text{ppm})$: 2.27(s, 3H, SCH_3); 6.89-7.46(m, 6H, NH, Ar, CH cycle).

$^{13}\text{C-NMR}$ ⁷ $\delta(\text{ppm})$: 12.46(c, SCH_3); 14.24(c, CH_3CH_2); 21.45(c, CH_3Ar); 61.72(t, CH_2CH_3); 123.34 (s, C5); 129.42, 130.19(d, $\text{C}2^-$, $\text{C}3^-$); 130.66(s, $\text{C}1^-$); 134.15(broad d, C2); 140.15(s, $\text{C}4^-$); 165.23(s, C4); 168.23(s, CO_2Et).

MS.m/e: 281(1.4); 280(3.6); 279(19.1); 232(14.3); 231(47.6); 186(34.1); 158(19.1); 131(100).

Ic ($\text{R}^1=\text{MeO}$; $\text{R}^2=\text{H}$).

IR⁵ $\nu(\text{cm}^{-1})$: 3210; 1700; 1645; 1600.

$^1\text{H-NMR}$ ⁶ $\delta(\text{ppm})$: 2.30(s, 3H, SCH_3); 6.69-7.68(m, 6H, NH, Ar, CH cycle).

$^{13}\text{C-NMR}$ ⁷ $\delta(\text{ppm})$: 12.51(c, SCH_3); 14.29(c, CH_3CH_2); 55.24(c, OCH_3); 61.66(t, CH_2CH_3); 114.23 (d, $\text{C}3^-$); 121.87(s, C5); 126.04(s, $\text{C}1^-$); 132.14(d, $\text{C}2^-$); 134.67(broad d, C2); 160.99(s, $\text{C}4^-$); 168.50(s, CO_2Et).

MS.m/e(%): 297(2.8); 295(37.0); 248(13.2); 247(65.5); 174(19.8); 147(100).

Id(R¹=C1;R²=H).

IR⁵_v(cm⁻¹): 3220; 1705;1645; 1585.

¹H-NMR⁶_δ(ppm): 2.28(s,3H,SCH₃); 7.02-7.84(m,6H,NH,Ar,CH cycle).

¹³C-NMR⁷_δ(ppm):12.39(c,SCH₃); 14.03(c,CH₃CH₂); 61.88(t,CH₂CH₃); 123.85(s,C5); 128.68(d,C3⁻); 130.89(d,C2⁻); 131.15(broad d,C2); 131.91(s,C4⁻); 135.46(s,C1⁻); 164.69 (s,C4); 167.52(s,CO₂Et).

MS.m/e(%): 301(5.2); 299(13.4); 252(10.5); 251(39.8); 206(21.9); 178(7.6); 153(35.9); 152(25.0); 151(100); 150(33.6).

Ie(R¹,R²= OCH₂O).

IR⁵_v(cm⁻¹): 3210; 1710; 1650; 1600.

¹H-NMR⁶_δ(ppm): 2.29(s,3H,SCH₃); 5.89(s,2H,OCH₂O); 6.58-7.46(m,5H,NH,Ar,CH cycle).

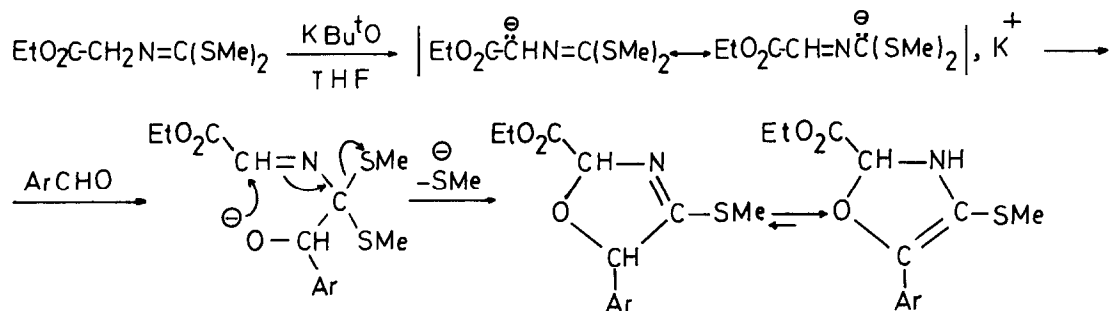
¹³C-NMR⁷_δ(ppm): 12.48(c,SCH₃); 14.29(c,CH₃CH₂); 61.72(t,CH₂CH₃); 101.62(t,OCH₂O); 108.43 (d,C2⁻); 109.29(d,C5⁻); 122.39(s,C5); 126.46(d,C6⁻); 127.61(s,C1⁻); 134.53 (broad d,C2); 148.09(s,C4⁻); 149.18(s,C3⁻); 165.33(s,C4); 168.50(s,CO₂Et).

MS.m/e(%): 309(37.3); 261(76.4); 188(17.6); 161(100); 160(78.6).

The low frequencies observed for ester carbonyl group can be justified by an intramolecular hydrogen bond between carbonyl and NH groups. The experimental values observed for 2-CH proton and carbon can be justified with bibliographic data of analogous compounds. It has been reported that H₂ proton of 5-aryl-4-methylthio-2,5-dihydrooxazol-5-ols appears at 5.6-5.9 ppm⁸. The deshielding contribution of ester group (~+1.35 ppm) justifies the experimental values. On the other hand, it has been reported that C2 carbon of 5-methoxy-4-phenyl-5-trifluoromethyl-2,5-dihydrooxazols⁹ appears at ~100 ppm. Contributions of ester group (~+22.6 ppm) and the change of sp²-N for sp³-N (~+8 ppm) justify the observed values.

In connection with the synthesis of oxazolines using a cyclocondensation reaction between a metallated nucleophile and carbonyl compounds it has been reported the synthesis of 2-oxazolines from α-alkali metallated isocyanides¹⁰ in a protic polar solvent and 2-alkylthio-2-oxazoline-4-carboxylates from αalkali metallated N-ethoxycarbonylmethylisothiocyanate¹¹ in an aprotic polar solvent.

The propensity of iminodithiocarbonates to undergo the metallation¹² together the presence of a potential leaving group (i.e. thiomethoxy) and the occurrence of an equilibrium imine-enamine, suggest the following reaction path:



NOTES AND REFERENCES.

- 1.- The methyl N-ethoxycarbonylmethyldithiocarbamate has been obtained according to method described for J.Garín, V.Martínez, J.Mayoral, E.Meléndez and F.Merchán, *Synthesis*, 961 (1981).
- 2.- Melting points are uncorrected.
- 3.- The THF is distilled from LiAlH₄.
- 4.- The spectra have been recorded with the following apparatus: IR: Perkin-Elmer, mod.256; ¹H- and ¹³C-NMR: Varian FT80-A; SM: Varian-Matt.
- 5.- KBr pellet.
- 6.- CDCl₃/TMS. Spectral width: 2000 Hz. Adquisition time: 1.023 s.
- 7.- CDCl₃/TMS. Spectral width: 5000 Hz. Adquisition time: 1.638 s. The multiplicity of signals has been determined from off-resonance spectra.
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- 10.-a)F.Gerhart and U.Schollkopf, *Tetrahedron Letters*, 6231(1968); b)U.Schollkopf, *Angew.Chem., Int.Ed.*, 9,763(1970); c)H.Oldenziel and A.M. van Leusen, *Tetrahedron Letters*, 2777(1972); d)U.Schollkopf, F.Gerhart, I.Hoppe, R.Harms, K.Hantke, K.H.Scheunemann, E.Eilers and E.Blume, *Liebigs Ann.Chem.*, 183(1976); e)U.Schollkopf, F.Gerhart, I.Hoppe, R.Harms, K.Hantke, K.H.Scheunemann, E.Eilers and E.Blume, *Ibid.*, 1183(1977).
- 11.-D.Hoppe, *Liebigs Ann.Chem.*, 1843(1976).
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