

Reactivity of Dimethyl *N*-(Ethoxycarbonylmethyl)iminodithiocarbonate with Carbonyl Compounds in Basic Medium

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The reactivity of dimethyl *N*-(ethoxycarbonylmethyl)iminodithiocarbonate with aromatic aldehydes and reactive ketones has been studied. Ethyl 3-aryl-2-(methylthiocarbonylamino)acrylates (**1**) are obtained with aromatic aldehydes by ring-opening isomerization of the intermediate 5-aryl-4-ethoxycarbonyl-2-methylthio-4,5-dihydro-1,3-oxazoles (**2**). With ketones it has been shown that the cycloalkanones give rise to the corresponding alkylidene derivatives by a reaction path identical with that of aromatic aldehydes, whereas hexafluoroacetone and 1,1,1-trifluoroacetone display duality in acting as both acylating reagents and carbonyl compounds.

α -Metallated alkyl isocyanides,¹ tosylmethyl isocyanides,² tosylmethyl-carbodi-imides,³ alkyl tosylmethyl imidates and thioimides,⁴ tosylmethyl iminocarbonates,⁵ and ethoxy-carbonylmethyl isothiocyanate⁶ have been used as synthetic equivalents of C(4)-N=C(2) synthons to prepare 1,3-oxazoles or 4,5-dihydro-1,3-oxazoles by condensation with carbonyl compounds in basic media.

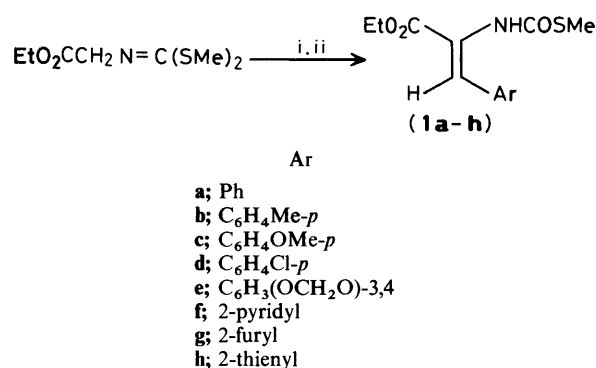
In seeking for a variation in the regiochemistry of these cyclocondensations, we have used dimethyl *N*-(ethoxycarbonylmethyl)iminodithiocarbonate, EMIC,^{7,8} the aza-allylic carbanion of which should show, in principle, a greater symmetrization of the negative charge under the influence of substituents on the 4- and 2-carbon atoms and affect the nature of the products obtained. Further, variations in the nature of the electrophiles used (arenecarbaldehydes and ketones) and of the reaction conditions can affect the relative degree to which competitive reaction paths occur and provide information about the reactivity of EMIC with carbonyl compounds.

Results and Discussion

Condensation with Aromatic Aldehydes.—Ethyl 3-aryl-2-(methylthiocarbonylamino)acrylates (**1**) have been obtained by reaction of EMIC with aromatic aldehydes at room temperature in the presence of potassium *t*-butoxide-tetrahydrofuran (Scheme 1). The results of these condensations are collected in Table 1. All the reactions were carried out with metallation of EMIC at -78°C . The ratio of reagents and the other variables were established after several experiments. The yields are unmodified by further increase of the base:EMIC ratio. The reaction mixtures contained unchanged aldehyde and EMIC as well as ethyl 3-aryl-2-(methylthiocarbonylamino)acrylates (**1**) as the only products.

Moreover, ^1H and ^{13}C n.m.r. spectra of the reaction mixtures demonstrate the formation of a single stereoisomer of the acrylates (**1a–h**) [except (**1g**)]. Although assignment of *Z* or *E* configuration could not be made from the spectroscopic data, it was established by chemical methods. The latter also showed that an earlier dihydro-oxazole (**3**) (Scheme 2)⁸ assignment was incorrect.

In fact, Makosza *et al.*⁹ suggested correct structural assignments for the acrylates (**1a**) and (**1d**) on the basis of an earlier report of compound (**1a**).⁶ Their conclusion has now been verified by preparation of the precursor 4,5-dihydro-1,3-oxazole (**2a**) (Scheme 2), by using the reaction conditions shown



Scheme 1. Reagents and conditions: i, KOBu^t, THF, -78°C , 0.5 h; ii, ArCHO, THF, -78°C for 0.5 h and 20°C for 2 h

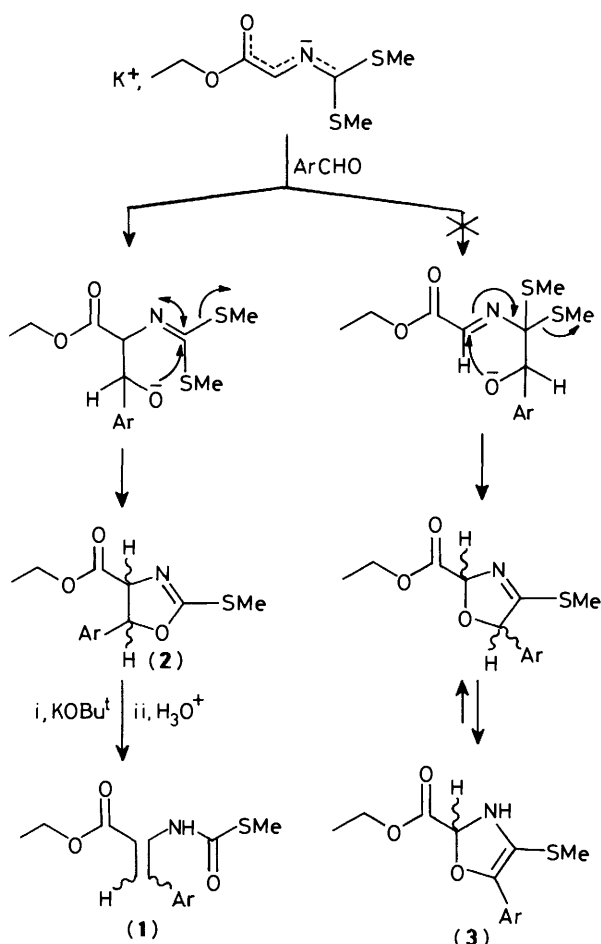
in Table 2 with benzaldehyde, pyridine-2-carbaldehyde, furan-2-carbaldehyde, and thiophene-2-carbaldehyde.

In spite of the low percentage conversion of EMIC, the dihydro-oxazole (**2**) was the only product detected in the reaction. An analysis of the AB systems formed by the 4- and 5-H protons of the dihydro-oxazole ring (**2a, f–h**), $J_{\text{AB}}(\text{cis}) = 8.0\text{--}10.8$ Hz; $J_{\text{AB}}(\text{trans}) = 6.0\text{--}7.8$ Hz^{9,10} leads to the unambiguous assignment of the dihydro-oxazole structure (**2**) as opposed to (**3**). Formation of these products is related to the two possible reaction paths of the aza-allylic anion derived from EMIC (Scheme 2). In all cases the *trans*:*cis* ratio was equal 3:1.

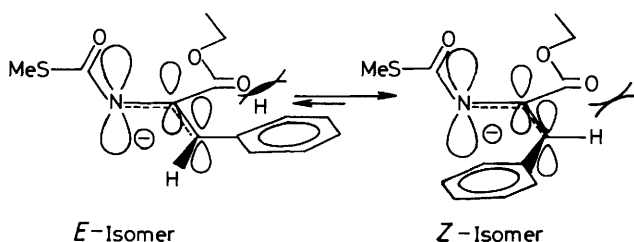
In a second experiment the transformation of the dihydro-oxazole (**2a**) into the acrylate (**1a**) was carried out with KOBu^t at room temperature. The i.r., ^1H n.m.r., ^{13}C n.m.r., and m.s. spectra of the resulting product were identical with those of the compound obtained without previous isolation of (**2a**). This result also verifies the regioselectivity pointed out by Makosza *et al.*,⁹ and the chemical path leading to the acrylates (**1**).

The net formation of a single *Z* or *E* stereoisomer of (**1a–f, h**) independently of the *trans*:*cis* ratio of the precursor 4,5-dihydro-1,3-oxazole (**2**) may result from *Z* – *E* equilibration in the conjugated base of the acrylates (**1**) (Scheme 3), steric inhibition of the resonance in the *E*-derivative displacing the equilibrium in favour of the *Z*-isomer.

Condensation with highly reactive ketones. Since attempted condensations between the α -metallated EMIC and low reactive ketones (*e.g.* acetophenone), gave negative results further experiments were performed with hexafluoroacetone, 1,1,1-



Scheme 2.



Scheme 3.

trifluoropropanone, and cycloalkanones (Scheme 4). Representative runs of these reactions have been gathered in Table 3. The isolation of the oxazole (5) and the thiocarbamate (7) supports the hypothesis that consecutive nucleophilic substitution of trifluoromethyl groups occurs.

The iminodithiocarbonate (4) results from a double acylation of the metallated EMIC through a reaction path that could be competitive with the formation of the 1,3-oxazole (5) and the thiocarbamate (6) (Scheme 5).

Formation of the intermediate 4,5-dihydro-1,3-oxazole (path b) explains the formation by a ring-opening isomerization of the acrylate (6).⁶ This acrylate is analogous to the acrylates (1) and its structure has been elucidated by ¹H and ¹³C n.m.r. spectroscopy. This same 4,5-dihydro-1,3-oxazole intermediate may also yield the oxazole (5) by an elimination step promoted by the basic medium, the ability of the trifluoromethyl as a good leaving group, and the double conjugation of the olefinic bond with the EtCO₂ and N=C groups. The 1,3-oxazole (5) has been characterized on the basis of its ¹H and ¹³C n.m.r. spectra. The

reaction paths to the 1,3-oxazole (5) from the monoacylated EMIC can be either alternate or competitive.

The structure of the thiocarbamate (7) has been established from its u.v., i.r., ¹H n.m.r., decoupled and coupled ¹³C n.m.r., mass and X-ray spectral results¹¹ and combustion microanalysis. The formation of the thiocarbamate (7) can be understood by retrosynthetic analysis (Scheme 6). The development of the synthetic equivalence of the synthon (C), as well as its origin from EMIC and its possible reaction with the salt of the enamine (E), indicates the strong electron withdrawing character of the gem-dimethylthiomethylene group. Thus, formation of the thiocarbamate (7) (Scheme 7) could be explained in terms of a condensation between (E) and the intermediate (11): (E) would be the condensation product between EMIC and the 1,1,1-trifluoropropanone, and the iminodithiocarbonate (11) is produced in a similar way to the dithiocarbonate (4) (Table 3, run 1).

Condensation of the intermediate (E) would be followed by a 1,2-acyl migration from carbon to nitrogen.¹² Evolution of the N-acylcarbanion (F) through an E1cB reaction¹³ gives rise to the imino derivatives (A) and (A'). Nucleophilic attack on the former by potassium methyl sulphide then leads to (7). Attempted isolation of a similar adduct from (A') proved unsuccessful.

α -Metallated EMIC condenses with cyclohexanone and cyclopentanone in a similar fashion to its reactions with aromatic aldehydes (Scheme 2). The results, however, are markedly dependent on the reaction conditions and only cyclohexanone is sufficiently reactive for cross-condensation to predominate over selfcondensation.

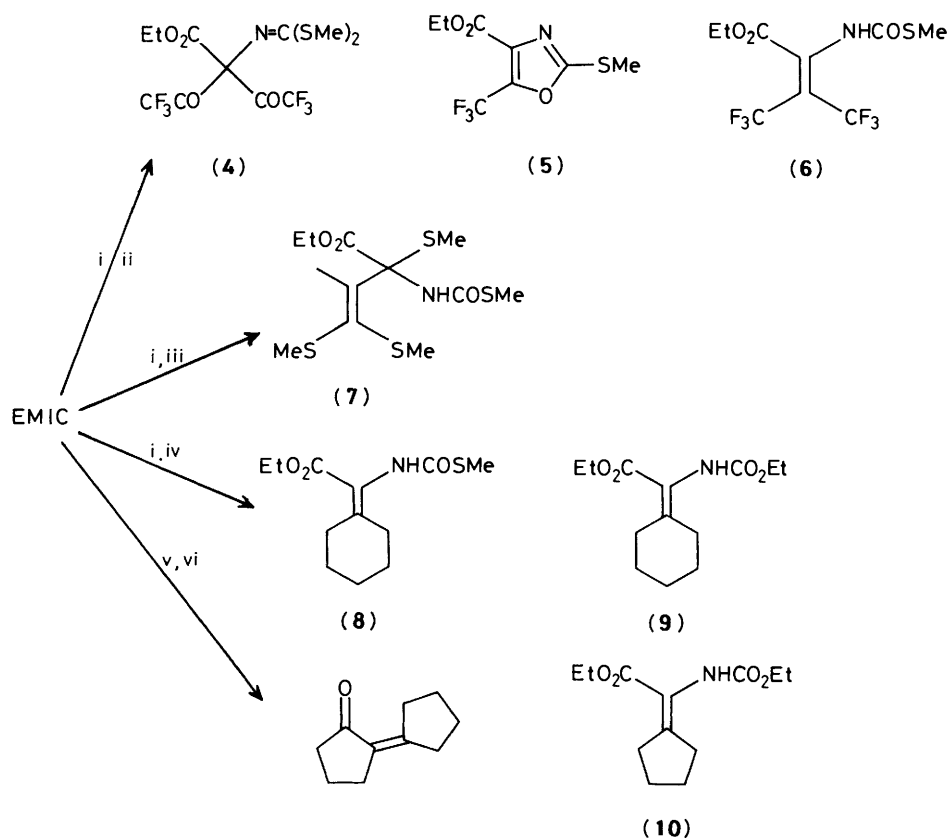
The acrylates (8) and (9) could be selectively obtained with the appropriate conditions (Table 3, runs 4 and 5, respectively). Thus, an unexpected transfunctionalization from the mono-thiocarbamate (8) to the ethyl carbamate (9) occurred when the α -metallated EMIC and cyclohexanone were condensed at 20 °C (Table 3, runs 3 and 5); at 0 °C the latter process did not occur (Table 3, run 4) and the acrylate (8) was selectively obtained in a good yield. The ethyl carbamate (9) could have originated from the acrylate (8) by transfunctionalization with the α -metallated EMIC that remains unchanged (Scheme 8). A similar process has been observed with cyclopentanone (Table 3, run 9) but only to a small extent.

The mass spectra of the acrylates (8) and (9) display interesting aspects. The molecular ion is absent and the key peaks of both compounds are identical. The fragmentation pattern of both molecular ions converges on an isocyanate (*m/z* 209) by elimination of thiomethanol from (8) or ethanol from (9). The loss of ethylene (*m/z* 181) and the ethyl radical (*m/z* 180) corroborate the presence of an ethoxycarbonyl group.¹⁴ The remaining ion fragmentation can be easily identified: loss of a hydroxyl radical and water from the *m/z* 181 ion, and loss of CO from the *m/z* 164 ion. The base peak corresponds to a loss of CO from the *m/z* 136 ion.

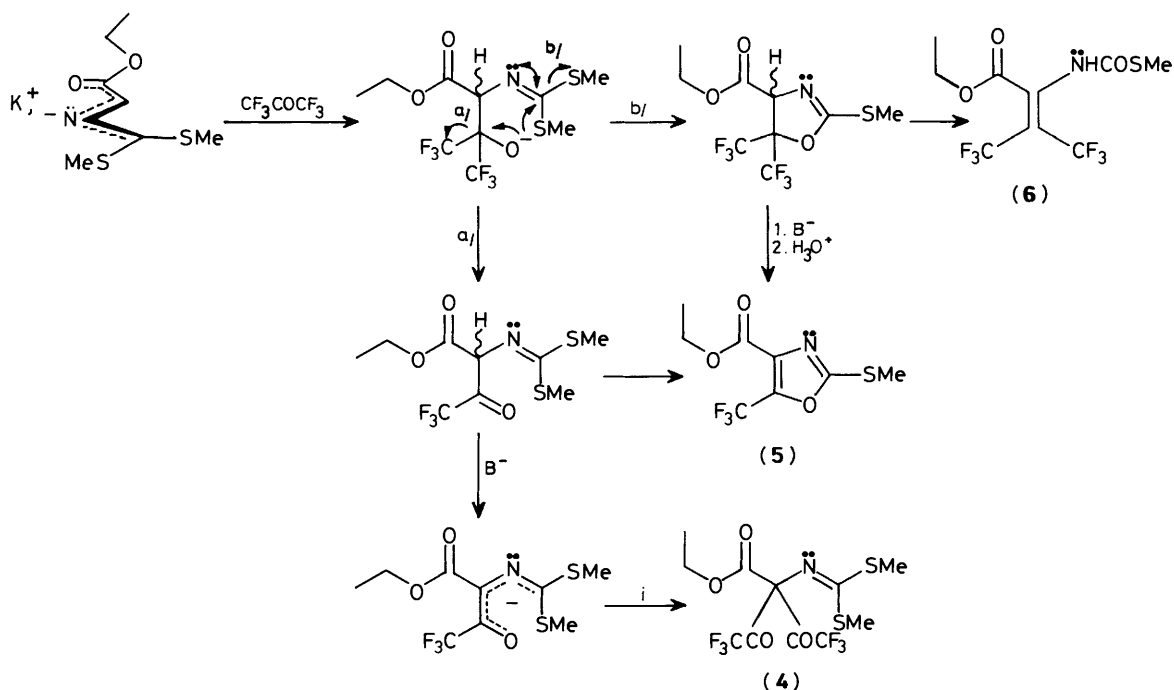
Experimental

M.p.s were determined with a Büchi 520 apparatus in capillary tubes and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 761 spectrophotometer. ¹H and ¹³C N.m.r. spectra were recorded on a Varian FT 80A spectrometer (79.542 MHz for ¹H and 20.00 MHz for ¹³C). Solutions in CDCl₃ (13% and 25% w/v, respectively) at 303 K were used. Chemical shifts are quoted in δ values using TMS as internal reference. ¹³C N.m.r. coupled spectra were recorded in some cases. Mass spectra were taken on a Varian Mat 711 spectrometer using the direct introduction probe. Pre-coated silica gel 60 F₂₅₄ plates (Merck) were used for t.l.c., and silica gel 273–400 mesh (Merck) was used for flash column chromatography.

EMIC^{7,8} was synthesized from ethyl glycinate hydrochloride



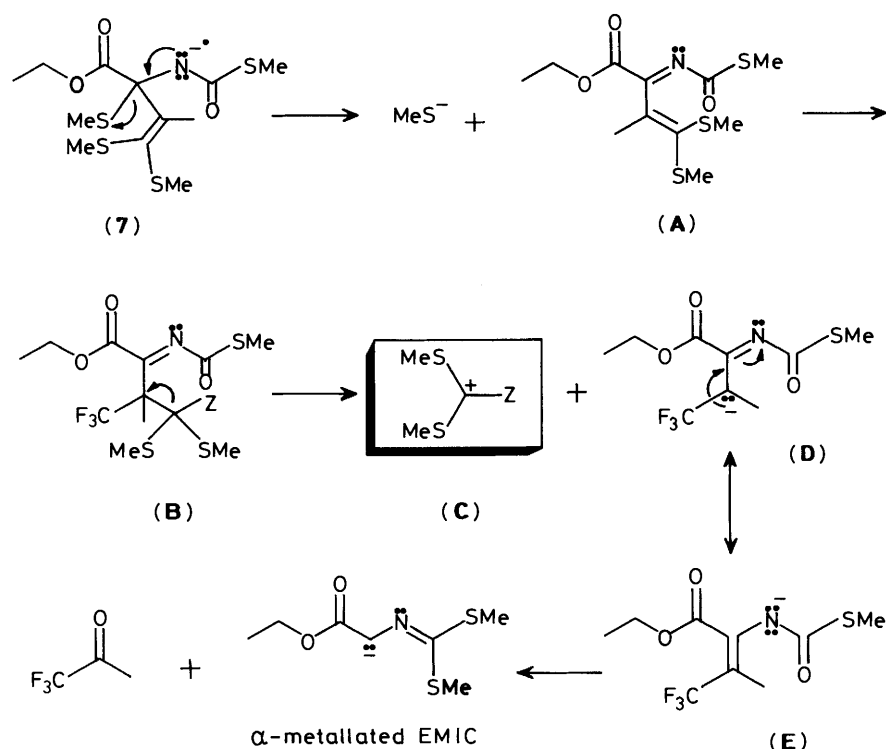
Scheme 4. Reagents and conditions: i, $KOBu^t$ -THF, $-78^\circ C$, 0.5 h; ii, $(CF_3)_2CO$ -THF, $0^\circ C$ for 2 h, $20^\circ C$ for 1.5 h; iii, CF_3COCH_3 -THF, $0^\circ C$ for 2 h, $20^\circ C$ for 1.5 h; iv, cyclohexanone-THF, $20^\circ C$ for 1.5 h; v, NaH-THF, $-78^\circ C$ for 0.5 h; vi, cyclopentanone-THF, $20^\circ C$ for 1.5 h



Scheme 5. Reagent: i, $(CF_3)_2CO$

(Aldrich Chemie), carbon disulphide, and methyl iodide following a published procedure.⁸ α -Metallated EMIC was allowed to react with aldehydes (Tables 1 and 2), and ketones (Table 3) in $KOBu^t$ -THF and NaH-THF systems using a variety of reaction conditions (Tables 1, 2, and 3). The products were isolated following a general procedure (see Tables 1–3).

General Procedure for Condensation of EMIC with Aldehydes and Ketones.—A solution of EMIC (1 g, 5 mmol) in dry THF (4 ml) was dropwise added to a stirred solution of $KOBu^t$ (0.85 g, 7.5 mmol) in dry THF (50 ml; kept at $-78^\circ C$ under N_2). After 0.5 h at $-78^\circ C$, a solution of aldehyde (7.5 mmol) in dry THF (4 ml) was slowly added. The reaction mixture was



Scheme 6.

Table 1. Yields of ethyl 3-aryl-2-(methylthiocarbonylamino)acrylates (**2**) obtained from EMIC and aromatic aldehydes with the $\text{KBu}^t\text{O}/\text{THF}$ system^a

Compd.	Ar	Yield (%) ^b	M.p. (°C)
(1a)	Ph	84	99–100
(1b)	<i>p</i> -MeC ₆ H ₄	66	75–77
(1c)	<i>p</i> -MeOC ₆ H ₄	54	71–72
(1d)	<i>p</i> -ClC ₆ H ₄	96	98–100
(1e)	3,4-(OCH ₂ O) ₆ H ₃	56	100–102
(1f)	2-Pyridyl	9 ^c	—
(1g)	2-Furyl	43	Liquid
(1h)	2-Thienyl	48	86–87

^a Metallation of EMIC: $-78^\circ\text{C}/0.5$ h. Condensation: $-78^\circ\text{C}/0.5$ h and $20^\circ\text{C}/2$ h. Ratio of reagents EMIC:base:aldehyde = 1:1.5:1.5.

^b Yield of isolated product from flash chromatography on silica gel. ^c 2.2 Equiv. of base were used. The product partially decomposes during the isolation process by flash chromatography on silica gel. However, it can be detected in the reaction mixture by ¹H n.m.r. spectroscopy.

kept at -78°C during 0.5 h, and then at room temperature for 2 h; it was then hydrolysed and extracted with diethyl ether (3×30 ml). The combined organic layers were dried (MgSO_4) and evaporated to dryness and the product was isolated by flash chromatography on silica gel [compounds (1a–h), Table 1; (2a) and (2f–h), Table 2; (4)–(6), (8)–(10), and 2-cyclohexylidene-cyclohexanone and 2-cyclopentylidene-cyclopentanone, Table 3], or by precipitation with pentane from the organic extract and recrystallization [compound (7), Table 3], or sublimation [compound (8), Table 3].

Preparation of compound (1a) from (2a). A solution of the reaction mixture [1.3 g; 26% in (2a)] obtained by reaction of EMIC and benzaldehyde at -78°C (Table 2, run 1) in dry THF (8 ml) was added dropwise to a stirred solution of KOBu^t (0.826 g, 0.736 mmol) in dry THF (100 ml; kept at -78°C under nitrogen). After 2 h at -78°C , the mixture was set aside at

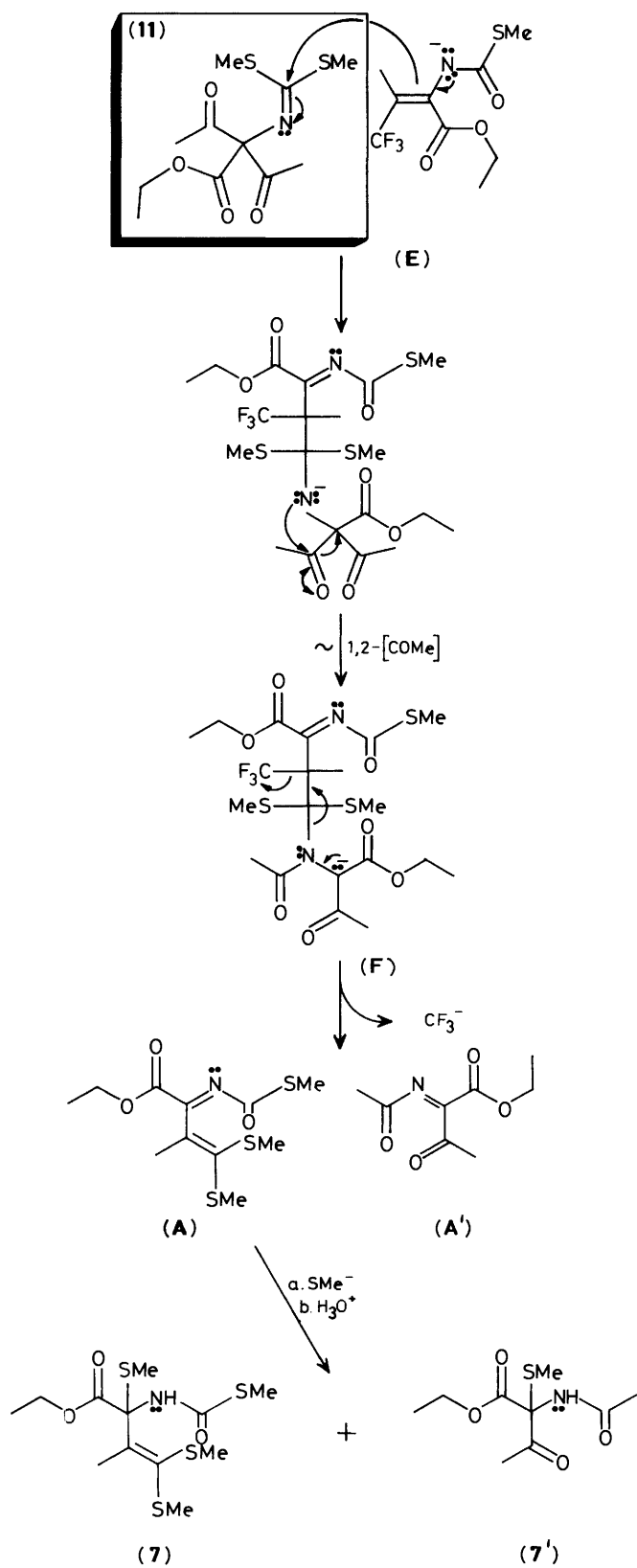
Table 2. Yields of 5-aryl-4-ethoxycarbonyl-2-methylthio-4,5-dihydro-1,3-oxazoles (**2**) obtained from EMIC and aromatic aldehydes^a

Compd. ^b	Ar	Yield (%) ^{c,d}
(2a)	Ph	55(30)
(2f)	2-Pyridyl	54(33)
(2g)	2-Furyl	(31)
(2h)	2-Thienyl	30 (5)

^a Metallation of EMIC with $\text{KBu}^t\text{O}/\text{THF}$ at $-78^\circ\text{C}/0.5$ h. Condensation with ArCHO at $-78^\circ\text{C}/3$ h. Reaction mixture hydrolysed at -78°C with methanol–water. Ratio EMIC:base:aldehyde = 1:1:1.5, except for (2h) (1:1.5:1.5). ^b Isolated and purified by flash chromatography on silica gel and preparative t.l.c. on silica gel. ^c Calculated from the ¹H n.m.r. spectra of the reaction mixtures: the yields refer to the product isolated (and purified). ^d Mixture of isomers (76% *trans*:24% *cis*).

room temperature for 2 h, and then was hydrolysed and extracted with diethyl ether (3×30 ml). The combined organic layers were dried (MgSO_4) and evaporated to dryness. The product (1a) (340 mg) was isolated by slow precipitation with cold pentane and purified by recrystallization (0.130 g, 66%), m.p. 99–100 °C (from hexane). The product obtained in this way had i.r., ¹H n.m.r., and ¹³C n.m.r. spectra and a chromatographic R_F value identical with those of compound (1a) obtained directly from EMIC and benzaldehyde (Table 1, run 1).

Ethyl 2-(methylthiocarbonylamino)-3-phenylacrylate (1a). This was isolated by flash chromatography with light petroleum–ethyl acetate (95:5) and purified by recrystallization; m.p. 99–100 °C (from hexane) (Found: C, 59.1; H, 5.8; N, 5.1; S, 12.1. $\text{C}_{13}\text{H}_{15}\text{NO}_3\text{S}$ requires C, 58.9; H, 5.7; N, 5.3; S, 12.1); ν_{max} (KBr pellet) 3 180, 3 100, 1 695, 1 650, 1 630, 1 250, and 1 100 cm^{-1} ; δ_{H} 1.29 (3 H, t, J 7.1 Hz, CH_3CH_2), 2.27 (3 H, s, SCH_3), 4.23 (2 H, q, J 7.1 Hz, CH_2CH_3), and 6.15–7.93 (7 H, m, NH, =CH, Ph); δ_{C} 12.5 (q, SCH_3), 14.2 (q, CH_3CH_2), 61.8 (t,



CH_2CH_3), 124.5 [s, $=\text{C}(\text{CO}_2\text{Et})\text{NHCOSCH}_3$], 128.6, 129.7, 130.0 (d, *o*-, *m*-, and *p*-C), 133.4 (s, *ipso*-C), 133.6 (br d, $=\text{CH}$), 165.1 (s, COSCH_3), and 168.1 (s, CO_2Et); m/z 267 (0.7%), 265 (8.7), 217 (35.1), 172 (23.0), 144 (13.5), and 117 (100).

Ethyl 2-(methylthiocarbonylamino)-3-(4-methylphenyl)acrylate (1b). This was isolated by flash chromatography with light petroleum–ethyl acetate (95:5–80:20) and purified by recrystallization; m.p. 75–77 °C (from hexane) (Found: C, 60.5; H, 6.25; N, 4.8; S, 11.4. $\text{C}_{14}\text{H}_{17}\text{NO}_3\text{S}$ requires C, 60.2; H, 6.1; N, 5.0; S, 11.5); ν_{max} (KBr pellet) 3 280, 3 100, 1 710, 1 640, 1 260, and 1 100 cm^{-1} ; δ_{H} 1.29 (3 H, t, J 7.1 Hz, CH_3CH_2), 2.27 (6 H, s, SCH_3 and CH_3Ar), 4.21 (2 H, q, J 7.1 Hz, CH_2CH_3), and 6.89–7.46 (6 H, m, NH, $=\text{CH}$, Ar); δ_{C} 12.5 (q, SCH_3), 14.2 (q, CH_3CH_2), 21.4 (q, CH_3Ar), 61.7 (t, CH_2CH_3), 123.3 [s, $=\text{C}(\text{CO}_2\text{Et})\text{NHCOSCH}_3$], 129.4 (d, *m*-C), 130.2 (d, *o*-C), 130.7 (s, *ipso*-C), 134.1 (br d, $=\text{CH}$), 140.1 (br s, *p*-C), 165.2 (s, COSMe), and 168.2 (s, CO_2Et); m/z 281 (1.4%), 280 (3.6), 279 (19.1), 232 (14.3), 231 (47.6), 186 (34.1), 158 (19.1), and 131 (100).

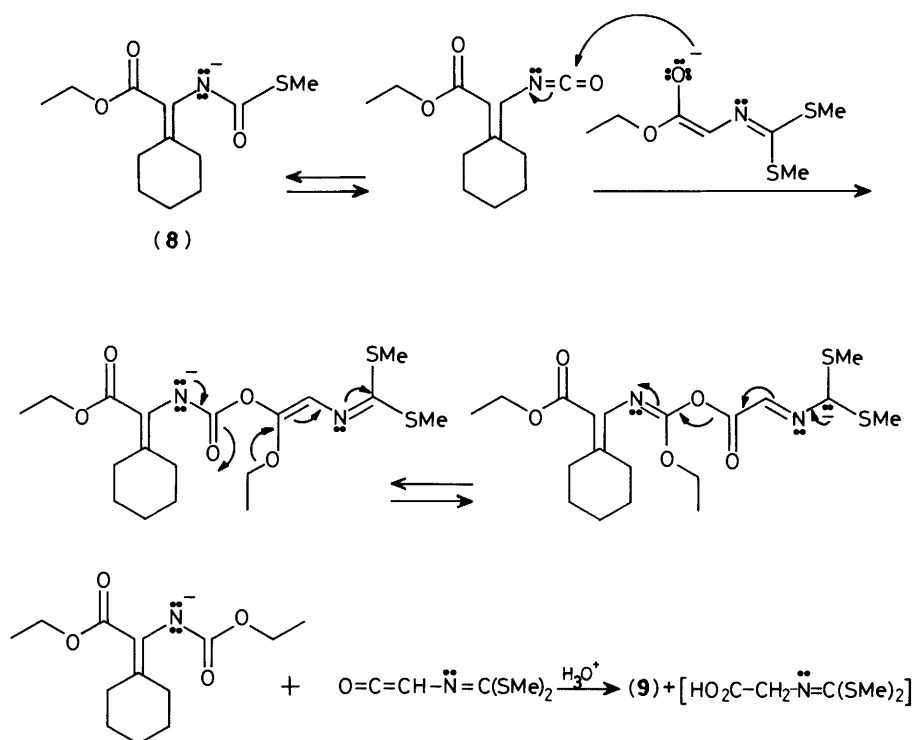
Ethyl 2-(methylthiocarbonylamino)-3-(4-methoxyphenyl)acrylate (1c). This was isolated by flash chromatography with light petroleum–ethyl acetate (95:5–80:20) and purified by recrystallization (twice); m.p. 71–72 °C (from light petroleum) (Found: C, 56.8; H, 5.8; N, 4.7; S, 10.6. $\text{C}_{14}\text{H}_{17}\text{NO}_4\text{S}$ requires C, 56.9; H, 5.8; N, 4.7; S, 10.8); ν_{max} (KBr pellet) 3 210, 3 020, 1 700, 1 645, 1 600, 1 270, and 1 170 cm^{-1} ; δ_{H} 1.31 (3 H, t, J 7.1 Hz, CH_3CH_2), 2.30 (3 H, s, SCH_3), 3.76 (3 H, s, OCH_3), 4.24 (2 H, q, J 7.1 Hz, CH_2CH_3), and 6.69–7.68 (6 H, m, NH, $=\text{CH}$, Ar); δ_{C} 12.5 (q, SCH_3), 14.3 (q, CH_3CH_2), 55.2 (q, OCH_3), 61.7 (t, CH_2CH_3), 114.2 (d, *m*-C), 121.9 [s, $=\text{C}(\text{CO}_2\text{Et})\text{HHCOSCH}_3$], 126.0 (br s, *ipso*-C), 132.1 (d, *o*-C), 134.7 (br d, $=\text{CH}$), 161.0 (br s, *p*-C), 165.4 (s, COSCH_3), and 168.5 (s, CO_2Et); m/z 297 (2.8%), 296 (6.6), 295 (37.0), 248 (13.2), 247 (65.5), 174 (19.8), and 147 (100.0).

Ethyl 3-(4-chlorophenyl)-2-(methylthiocarbonylamino)acrylate (1d). This was isolated by flash chromatography with light petroleum–ethyl acetate (95:5–80:20) and purified by recrystallization (twice); m.p. 98–100 °C (from light petroleum) (Found: C, 52.3; H, 4.8; Cl, 12.1; N, 4.5; S, 11.0. $\text{C}_{13}\text{H}_{14}\text{ClNO}_3\text{S}$ requires C, 52.05; H, 4.7; Cl, 11.85; N, 4.7; S, 10.7); ν_{max} (KBr pellet) 3 220, 3 100, 1 705, 1 645, 1 585, 1 260, and 1 080 cm^{-1} ; δ_{H} 1.30 (3 H, t, J 6.8 Hz, CH_3CH_2), 2.28 (3 H, s, SCH_3), 4.25 (2 H, q, J 6.8 Hz, CH_2CH_3), and 7.02–7.84 (6 H, m, NH, $=\text{CH}$, Ar); δ_{C} 12.4 (q, SCH_3), 14.0 (q, CH_3CH_2), 61.9 (t, CH_2CH_3), 123.8 [s, $=\text{C}(\text{CO}_2\text{Et})\text{NHCOSMe}$], 128.7 (d, *m*-C), 130.9 (d, *o*-C), 131.1 (br d, $=\text{CH}$), 131.9 (s, *p*-C), 135.5 (s, *ipso*-C), 164.7 (s, COSMe), and 167.5 (s, CO_2Et); m/z 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 (100.0), and 150 (33.6).

Ethyl 3-(3,4-methylenedioxyphenyl)-2-(methylthiocarbonylamino)acrylate (1e). This was isolated by flash chromatography with light petroleum–ethyl acetate (95:5–80:20) and purified by recrystallization (twice); m.p. 100–102 °C (from light petroleum) (Found: C, 54.3; H, 4.9; N, 4.4; S, 10.2. $\text{C}_{14}\text{H}_{15}\text{NO}_5\text{S}$ requires C, 54.4; H, 4.85; N, 4.5; S, 10.35); ν_{max} (KBr pellet) 3 210, 3 100, 1 710, 1 650, 1 600, 1 200, and 1 040 cm^{-1} ; δ_{H} 1.34 (3 H, t, J 7.2 Hz, CH_3CH_2), 2.29 (3 H, s, SCH_3), 4.24 (2 H, q, J 7.2 Hz, CH_2CH_3), 5.89 (2 H, s, OCH_2O), and 6.58–7.46 (5 H, m, NH, $=\text{CH}$, Ar); δ_{C} 12.5 (q, SCH_3), 14.3 (q, CH_3CH_2), 61.7 (t, CH_2CH_3), 101.6 (t, OCH_2O), 109.3 (d, 5'-C), 122.4 [s, $=\text{C}(\text{CO}_2\text{Et})\text{NHCOSMe}$], 126.5 (d, 6'-C), 127.6 (s, 1'-C), 134.5 (br d, $=\text{C}$), 148.1 (s, 4'-C), 149.2 (s, 3'-C), 165.3 (s, COSMe), and 168.5 (s, CO_2Et); m/z 309 (37.3%), 261 (76.4), 216 (24.5), 188 (17.6), 161 (100.0), and 160 (78.6).

Ethyl 2-(methylthiocarbonylamino)-3-(2'-pyridyl)acrylate (1f). Attempts to isolate the components by flash chromatography with light petroleum–ethyl acetate (70:30) were unsuccessful since the acrylate (1f) decomposed. Nevertheless, olefinic hydrogen signals were clearly observed in the ^1H n.m.r. spectrum of the reaction mixture and the yield of (1f) was calculated as 9% from the integration curve.

Ethyl 3-(2'-furyl)-2-(methylthiocarbonylamino)acrylate (1g).



Scheme 8.

Table 3. Condensation experiments of α -metallated EMIC with highly reactive ketones

Run	Ketone	EMIC: Base: Ketone ratio	Products	Yield (%)
1 ^a	Hexafluoroacetone	1:2:1.5	(4), (5), (6)	8, 5, 3
2 ^a	1,1,1-Trifluoropropanone	1:2:1.5	(7)	30
3 ^b	Cyclohexanone	1:2.2:1.5	(8), (9)	30, 35
4 ^c	Cyclohexanone	1:1:1	(8)	70
5 ^d	Cyclohexanone	1:2:1.5	(9)	13
6 ^b	Cyclohexanone	1:6:1.2	2-Cyclohexylidenecyclohexanone	50
7 ^e	Cyclopentanone	1:1:1	—	—
8 ^b	Cyclopentanone	1:2.2:1.5	2-Cyclopentylidenecyclopentanone	50
9 ^f	Cyclopentanone	1:3.2:1.5	2-Cyclopentylidenecyclopentanone (10)	28, 3

^a α -Metallation of EMIC with KBu^tO/THF at $-78^\circ C/0.5$ h. Condensation at $0^\circ C/2$ h and $20^\circ C/1.5$ h. ^b α -Metallation of EMIC just as *a*. Condensation at $20^\circ C/1.5$ h. ^c α -Metallation of EMIC just as *a*. Condensation at $0^\circ C/0.5$ h. ^d α -Metallation of EMIC with NAH/THF at $-78^\circ C/0.5$ h. Condensation at $-78^\circ C/0.5$ h and $20^\circ C/1.5$ h. ^e Reaction just as *c* but the condensation was attempted at $-78^\circ C/3$ h with negative results. ^f α -Metallation of EMIC with $NaH-THF$.

This was isolated as a liquid by flash chromatography with light petroleum–ethyl acetate (80:20) (Found: C, 51.7; H, 5.2; N, 5.3; S, 12.3. $C_{11}H_{13}NO_4S$ requires C, 51.8; H, 5.1; N, 5.5; S, 12.5); ν_{max} (neat) 3 400, 3 260, 3 180, 1 710, 1 680, 1 640, 1 220, and 1 180 cm^{-1} ; δ_H (as a mixture of the two isomers *Z-E*) 1.19 (3 H, t, *J* 6.9 Hz, CH_3CH_2), 1.31 (3 H, t, *J* 7.2 Hz, CH_3CH_2), 2.36 (3 H, s, SCH_3), 2.41 (3 H, s, SCH_3), 3.67 (2 H, q, *J* 6.9 Hz, CH_2CH_3), 6.26 (1 H, dd, *J* 4.0, 2.0 Hz, 3'-H, furyl), 6.64 (1 H, dd, *J* 4.0, 2.0 Hz, 4'-H, furyl), 7.10 (1 H, s, olefinic H), 7.30 (1 H, d, *J* 2.0 Hz, 5'-H, furyl), 7.44 (2 H, br s, NH), and 7.49 (1 H, d, *J* 2.0 Hz, 4'-H, furyl); δ_C 12.5 (SCH_3), 14.2 (CH_3CH_2), 61.7 (CH_2CH_3), 112.5, 115.8 (2'-C, 3'-C, furyl), 119.15 [$=C(CO_2Et)NHCOSMe$], 122.1 ($=CH$), 144.8 (4'-C, furyl), 149.5 (1'-C, furyl), and 164.6, 167.75 (CO_2Et , $NHCOSMe$).

Ethyl 2-(methylthiocarbonylamino)-3-(2'-thienyl)acrylate (1h).

This was isolated by precipitation with cold pentane and diethyl ether and purified by recrystallization; m.p. $86-87^\circ C$ (from hexane) (Found: C, 48.9; H, 4.6; N, 5.3; S, 23.4. $C_{11}H_{13}NO_3S_2$ requires C, 48.7; H, 4.8; N, 5.2; S, 23.6); ν_{max} (KBr) 3 180, 3 080, 1 700, 1 660, 1 630, 1 230, and 1 200 cm^{-1} ; δ_H 1.31 (3 H,

q, *J* 7.0 Hz, CH_3CH_2), 2.33 (3 H, s, SCH_3), 4.29 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 6.72 (1 H, br s, NH), 6.92–7.52 (3 H, m, 3'-H, 4'-H, 5'-H, thienyl), and 7.75 (1 H, s, $=CH$). δ_C 12.4 (CH_3CH_2), 14.2 (SCH_3), 61.6 (CH_2CH_3), 121.1 ($=CH$), 127.2 (2'-C, thienyl), 131.7 (4'-C, thienyl), 133.7 (3'-C, thienyl), 136.1 (1'-C, thienyl), 164.8 [$=C(CO_2Et)NHCOSMe$], and 169.4, 169.9 (CO_2Et , $NHCOSCH_3$).

4-Ethoxycarbonyl-2-methylthio-5-phenyl-4,5-dihydro-1,3-oxazole (2a). This was isolated by flash chromatography with light petroleum–ethyl acetate (80:20) followed by preparative t.l.c. with chloroform–hexane (97:3). *cis*-Isomer: ν_{max} ($CHCl_3$) 3 030, 3 020, 1 750, 1 720, 1 600, 1 570, 1 550, 1 180, and 1 140 cm^{-1} ; δ_H 0.79 (3 H, t, *J* 7.3 Hz, CH_3CH_2), 2.56 (3 H, s, SCH_3), 3.62 (2 H, q, *J* 7.3 Hz, CH_2CH_3), 5.06 (1 H, 1/2 AB, *J* 10.8 Hz, 4-H), 5.83 (1 H, 1/2 AB, *J* 10.8 Hz, 5-H), and 7.35 (5 H, br s, Ph). δ_C 13.6 (CH_3CH_2), 14.5 (SCH_3), 60.9 (CH_2CH_3), 73.2 (5-C), 84.8 (4-C), 126.4 (*m*-C), 128.2 (*o*-C), 128.8 (*p*-C), 135.4 (*ipso*-C), 168.9 (2-C), and 170.0 (CO_2Et).

trans-Isomer: ν_{max} ($CHCl_3$) 3 060, 3 020, 1 740, 1 720, 1 600, 1 590, 1 490, 1 190, and 1 150 cm^{-1} ; δ_H 1.29 (3 H, t, *J* 7.6 Hz,

CH_3CH_2), 2.49 (3 H, s, SCH_3), 4.27 (2 H, q, J 7.6 Hz, CH_2CH_3), 4.62 (1 H, 1/2 AB, J 7.8 Hz, 4-H), 5.77 (1 H, 1/2 AB, J 7.8 Hz, 5-H), and 7.34 (5 H, br s, Ph); δ_{C} 13.9 (CH_3CH_2), 14.2 (SCH_3), 61.6 (CH_2CH_3), 76.1 (5-C), 85.0 (4-C), 125.4 (*m*-C), 128.6, 128.7 (*o*-C, *p*-C), 138.7 (*ipso*-C), 168.5 (2'-C), and 170.3 (CO_2Et).

4-Ethoxycarbonyl-2-methylthio-5-(2'-pyridyl)-4,5-dihydro-1,3-oxazole (2f). This was isolated by flash chromatography with light petroleum-ethyl acetate (70:30). *cis*-Isomer: ν_{max} (CHCl_3) 3 060, 3 020, 1 750, 1 710, 1 600, 1 580, 1 560, 1 210, and 1 160 cm^{-1} ; δ_{H} 0.88 (3 H, t, J 7.1 Hz, CH_3CH_2), 2.59 (3 H, s, SCH_3), 3.74 (2 H, q, J 7.1 Hz, CH_2CH_3), 5.16 (1 H, 1/2 AB, J 10.0 Hz, 4-H), 5.91 (1 H, 1/2 AB, J 10.0 Hz, 5-H), 7.04–7.90 (3 H, m, 3'-H, 4'-H, and 5'-H, pyridine), and 8.43 (1 H, m, 6'-H, pyridine); δ_{C} 13.7 (CH_3CH_2), 14.6 (SCH_3), 60.9 (CH_2CH_3), 72.7 (5-C), 84.9 (4-C), 121.1 (3'-C, pyridine), 123.3 (5'-C, pyridine), 136.7 (4'-C, pyridine), 149.0 (6'-C, pyridine), 156.1 (2'-C, pyridine), 168.9 (2-C), and 169.8 (CO_2Et).

trans-Isomer: ν_{max} (CHCl_3) 3 080, 3 020, 1 740, 1 710, 1 600, 1 590, 1 570, 1 220, and 1 190 cm^{-1} ; δ_{H} 1.31 (3 H, t, J 7.0 Hz, CH_3CH_2), 2.53 (3 H, s, SCH_3), 4.28 (2 H, q, J 7.0 Hz, CH_2CH_3), 4.98 (1 H, 1/2 AB, J 6.4 Hz, 4-H), 5.91 (1 H, 1/2 AB, J 6.4 Hz, 5-H), 7.18–7.83 (3 H, m, 3'-H, 4'-H, and 5'-H, pyridine), and 8.61 (1 H, m, 6'-H, pyridine). δ_{C} 14.1 (CH_3CH_2), 14.5 (SCH_3), 61.8 (CH_2CH_3), 74.4 (5-C), 84.5 (4-C), 121.0 (3'-C, pyridine), 123.5 (5'-C, pyridine), 137.0 (4'-C, pyridine), 149.9 (6'-C, pyridine), 157.3 (2'-C, pyridine), 168.3 (2-C), and 170.5 (CO_2Et).

4-Ethoxycarbonyl-5-(2'-furyl)-2-methylthio-4,5-dihydro-1,3-oxazole (2g). This was isolated by flash chromatography with light petroleum-ethyl acetate (80:20). *cis*-Isomer: ν_{max} (CHCl_3) 3 020, 1 730, 1 660, 1 540, 1 500, 1 210, and 1 180 cm^{-1} ; δ_{H} 1.30 (3 H, t, J 7.5 Hz, CH_3CH_2), 2.46 (3 H, s, SCH_3), 4.26 (2 H, q, J 7.5 Hz, CH_2CH_3), 4.92 (1 H, 1/2 AB, J 7.96 Hz, 4-H), 5.82 (1 H, 1/2 AB, J 7.96 Hz, 5'-H), 6.31–6.57 (2 H, m, 3'-H and 4'-H, furyl), and 7.45 (1 H, m, 5'-H, furyl); δ_{C} 14.1 (CH_3CH_2), 14.4 (SCH_3), 61.9 (CH_2CH_3), 72.3 (5-C), 78.2 (4-C), 110.4, 110.7 (3'-C, 4'-C, furyl), 144.0 (2'-C, furyl), 149.7 (5'-C, furyl), 168.4 (2-C), and 170.1 (CO_2Et).

trans-Isomer: ν_{max} (CHCl_3) 3 010, 1 730, 1 670, 1 510, 1 210, and 1 180 cm^{-1} ; δ_{H} 1.26 (3 H, t, J 7.4 Hz, CH_3CH_2), 2.44 (3 H, s, SCH_3), 4.15 (2 H, q, J 7.4 Hz, CH_2CH_3), 4.81 (1 H, 1/2 AB, J 7.0 Hz, 4-H), 5.68 (1 H, 1/2 AB, J 7.0 Hz, 5-H), 6.13–6.42 (2 H, m, 3'-H, 4'-H, furyl), and 7.30 (1 H, m, 5'-H, furyl).

4-Ethoxycarbonyl-2-methylthio-5-(2'-thienyl)-4,5-dihydro-1,3-oxazole (2h). This was isolated by flash chromatography with light petroleum-ethyl acetate (80:20), followed by preparative t.l.c. with light petroleum-ethyl acetate (70:30). Mixture of *cis-trans* isomers: δ_{H} 0.94 (3 H, t, J 8.0 Hz, CH_3CH_2 , *cis*), 1.25 (3 H, t, J 7.5 Hz, CH_3CH_2 , *trans*), 2.52 (3 H, s, SCH_3 , *cis*), 2.57 (3 H, s, SCH_3 , *trans*), 3.83 (2 H, q, J 8.0 Hz, CH_2CH_3 , *cis*), 4.22 (2 H, q, J 7.5 Hz, CH_2CH_3 , *trans*), 4.72 (1 H, 1/2 AB, J 6.0 Hz, 4-H, *trans*), 5.00 (1 H, 1/2 AB, J 10.0 Hz, 4-H, *cis*), 5.97 (1 H, 1/2 AB, J 6.0 Hz, 5-H, *trans*), 6.04 (1 H, 1/2 AB, J 10.0 Hz, 5-H, *cis*), and 6.82–7.38 (6 H, m, thienyl ring, *cis* and *trans*).

Dinethyl [bis(trifluoromethylcarbonyl)ethoxycarbonylmethyl]iminodithiocarbonate (4) and 4-ethoxycarbonyl-2-methylthio-5-trifluoromethyl-1,3-oxazole (5). This was isolated together in a 3:2 ratio (4):(5) by flash chromatography with light petroleum-ethyl acetate (70:30), and characterized from the ^1H and ^{13}C n.m.r. spectra of the mixture: δ_{H} 1.26 [3 H, t, J 7.6 Hz, CH_3CH_2 (5)], 1.34 [3 H, t, J 7.0 Hz, CH_3CH_2 (4)], 2.05 [3 H, s, SCH_3 (5)], 2.43 [6 H, s, SCH_3 (4)], 4.00 [2 H, q, J 7.6 Hz, CH_2CH_3 (5)], and 4.34 [2 H, q, J 7.0 Hz, CH_2CH_3 (4)]; δ_{C} 12.8, 13.9, 14.2, 17.6, 20.9 [CH_3CH_2 and SCH_3 of (4) and (5)], 60.6 [CH_2CH_3 (5)], 63.4 [CH_2CH_3 (4)], 77.4 [quaternary C of (4)], 118.0 [q, $^1J(^{13}\text{C}, ^{19}\text{F})$ 288.5 Hz, CF_3 of (5)], 121.0 [q, $^1J(^{13}\text{C}, ^{19}\text{F})$ 275.4 Hz, CF_3 of (4)], 152.9 [q, $^3J(^{13}\text{C}, ^{19}\text{F})$ 1.22 Hz, 4-C, oxazole ring of (5)], 156.6 [q, $^2J(^{13}\text{C}, ^{19}\text{F})$ 2.77 Hz, 5-C, oxazole ring of (5)], 171.6 [CO_2Et , (4) and (5)], and 179.9 [COCF_3 (4)].

Ethyl 3,3-[bis(trifluoromethyl)]-2-(methylthiocarbonylamino)acrylate (6). This was isolated as a liquid by flash chromatography with light petroleum-ethyl acetate (70:30); ν_{max} (neat) 3 300, 1 720, 1 710, and 1 650 cm^{-1} ; δ_{H} 1.28 (3 H, t, J 7.0 Hz, CH_3CH_2), 2.06 (3 H, s, SCH_3), 4.13 (2 H, q, J Hz, 7.0 Hz, CH_2CH_3), 5.23 (1 H, br s, NHCOSMe); δ_{C} 20.0, 20.9 (CH_3CH_2 , NHCOSCH_3), 61.4 (CH_2CH_3), 92.4 [seven signals, $^2J(^{13}\text{C}, ^{19}\text{F})$ 34.0 Hz, $=\text{C}(\text{CF}_3)_2$], 120.8 [q, $^1J(^{13}\text{C}, ^{19}\text{F})$ 288.3 Hz, CF_3], and 173.2 (CO_2Et , NHCOSCH_3).

Ethyl 3-methyl-2,4,4-trimethylthio-2-(methylcarbonylamino)but-3-enoate (7). This was isolated from the reaction mixture by precipitation with pentane and purified by recrystallization; m.p. 114–116 °C (from hexane-ethyl acetate) (Found: C, 40.4; H, 6.0; N, 3.7; S, 36.4. $\text{C}_{12}\text{H}_{21}\text{NO}_3\text{S}_4$ requires C, 40.6; H, 5.9; N, 3.9; S, 36.1); λ_{max} (EtOH) 214.6 (ϵ 3 883 $\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$) and 262.5 nm (7 479); ν_{max} (KBr) 3 375, 1 712, 1 680, and 710 cm^{-1} ; δ_{H} 1.28 (3 H, t, J 7.9 Hz, CH_3CH_2), 2.00 (3 H, s, $\text{CH}_3\text{C}=\text{C}$), 2.18 (3 H, s, $\text{C}-\text{SCH}_3$), 2.26 (3 H, s), 2.33 [3 H, s, $=\text{C}(\text{SCH}_3)_2$], 2.49 (3 H, s, NHCOSCH_3), 4.22 (2 H, q, J 7.9 Hz, CH_2CH_3), and 7.14 (1 H, br s, NH); δ_{C} 12.4 (NHCOSCH_3), 13.0 (CH_3CH_2), 14.0 ($\text{C}-\text{SCH}_3$), 16.9, 17.1 [$=\text{C}(\text{SCH}_3)_2$], 21.0 ($=\text{C}-\text{CH}_3$), 62.6 (CH_2CH_3), 70.0 (quaternary C), 132.9 [$=\text{C}(\text{SMe})_2$], 142.2 ($=\text{C}-\text{CH}_3$), 164.5 (NHCOSCH_3), and 168.7 (CO_2Et); m/z 355 (1.1%), 310 (13.0), 309 (12.5), 308 (100.0), 292 (3.9), 280 (2.7), 265 (2.5), 262 (4.1), 261 (4.1), 260 (36.4), 234 (2.5), 232 (8.2), 206 (10.3), 184 (29.5), 130 (8.0), and 75 (31.8).

S-Methyl N-[Cyclohexylidene(ethoxycarbonyl)methyl] Thiocarbamate (8).—This was isolated and purified from the reaction mixture by preparative t.l.c. with hexane-ethyl acetate (60:40); m.p. 117–118 °C; ν_{max} (KBr) 3 300, 1 710, 1 630, 1 500, 1 300, 1 220, and 1 100 cm^{-1} ; δ_{H} 1.30 (3 H, t, J 7.0 Hz, CH_3CH_2), 1.64 (6 H, m, cyclohexane), 2.34–2.76 (7 H, m, NHCOSCH_3 and cyclohexane H), 4.22 (2 H, q, J 7.0, CH_2CH_3), and 6.70 (1 H, br s, NH); δ_{C} 12.5 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 14.2 (NHCOSCH_3), 26.1, 27.6, 27.7 (3'-C, 4'-C, 5'-C cyclohexane), 30.7, 31.8 (2'-C, 6'-C, cyclohexane), 60.9 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 118.4, 118.5 (olefinic C), and 164.8, 165.6 (CO_2Et , NHCOSMe); m/z 209 (52.0%), 181 (23.1), 180 (20.8), 164 (4.6), 163 (10.7), 136 (10.9), 109 (16.3), and 108 (100.0).

Ethyl N-[cyclohexylidene(ethoxycarbonyl)methyl] carbamate (9). This was isolated by flash chromatography with hexane-ethyl acetate (60:40) and purified by sublimation; m.p. 42–44 °C (Found: C, 61.3; H, 8.0; N, 5.3. $\text{C}_{15}\text{H}_{21}\text{NO}_4$ requires C, 61.2; H, 8.2; N, 5.5); ν_{max} (KBr) 3 290, 1 715, 1 690, 1 660, 1 260, and 1 180 cm^{-1} ; δ_{H} 1.24 (3 H, t, J 7.0 Hz), 1.29 (3 H, t, J 7.0 Hz) ($\text{CH}_3\text{CH}_2\text{OCO}$, $\text{CH}_3\text{CH}_2\text{OCONH}$), 1.60 (6 H, m, 3'-H, 4'-H, 5'-H, cyclohexane), 2.10–2.46 (2 H, m, 2'-H, 6'-H, axial H, cyclohexane), 2.50–2.80 (2 H, m, 2'-H, 6'-H, equatorial H, cyclohexane), 4.12 (2 H, q, J 7.0 Hz), 4.19 (2 H, q, J 7.0 Hz, $\text{CH}_3\text{CH}_2\text{OCO}$, $\text{CH}_3\text{CH}_2\text{OCONH}$), and 6.06 (1 H, br s, NH); δ_{C} 13.9, 14.2 ($\text{CH}_3\text{CH}_2\text{OCO}$, $\text{CH}_3\text{CH}_2\text{OCONH}$), 25.9 (4'-C, cyclohexane ring), 27.1, 27.5 (3'-C, 5'-C, cyclohexane), 30.2, 30.8 (2'-C, 6'-C, cyclohexane), 60.4, 61.0 ($\text{CH}_3\text{CH}_2\text{OCO}$, $\text{CH}_3\text{CH}_2\text{OCONH}$), 118.8 [$=\text{C}(\text{CO}_2\text{Et})$], 149.2 ($=\text{C}$ cyclohexylidene), 155.0 (NHCO_2Et), and 165.1 (CO_2Et); m/z 209 (44.5%), 181 (21.1), 180 (19.3), 164 (4.3), 163 (9.3), 136 (15.9), 109 (12.2), and 108 (100).

Ethyl N-[cyclopentylidene(ethoxycarbonyl)methyl] carbamate (10). This was isolated as a liquid by flash chromatography with light petroleum-ethyl acetate (70:30); ν_{max} (neat) 3 330, 3 300, 1 730, 1 710, 1 650, 1 230, and 1 190 cm^{-1} ; δ_{H} 1.24 (3 H, t, J 7.0 Hz), 1.28 (3 H, t, J 7.0 Hz) ($\text{CH}_3\text{CH}_2\text{OCO}$, $\text{CH}_3\text{CH}_2\text{OCONH}$), 1.41–1.80 (8 H, m, cyclopentane), 4.14 (2 H, q, J 7.0 Hz), 4.21 (2 H, q, J 7.0 Hz) ($\text{CH}_3\text{CH}_2\text{OCO}$, $\text{CH}_3\text{CH}_2\text{OCONH}$), and 6.04 (1 H, br s, NH); δ_{C} 12.6, 12.9 ($\text{CH}_3\text{CH}_2\text{OCO}$, $\text{CH}_3\text{CH}_2\text{OCONH}$), 25.3, 26.9 (3'-C, 4'-C, cyclopentane), 33.1, 33.8 (2'-C, 5'-C, cyclopentane), 60.6, 61.2

(CH₃CH₂OCO, CH₃CH₂OCONH), 117.9 [=C(CO₂Et)NH-CO₂Et], 154.6 (1'-C, cyclohexylidene), 159.8 (NHCO₂Et), and 164.8 (CO₂Et).

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