AN EFFICIENT SYNTHESIS OF 5-ARYL (OR ALKYL)AMINO-4-ETHOXYCARBONYL-2-METHYLTHTHO-1,3-
THIAZoles FROM DIMETHYL N-(ETHOXYCARBONYLMETHYL)IMINODITHIOCARBONATE AND
ISOThIOCYANATES.

Carlos Alvarez-Ibarra, Matilde Gil, Paloma Ortiz, and Maria L. Guirroga.
Departamento de Química Orgánica I. Facultad de Química. Universidad Complutense.
28040 Madrid. España.

Abstract—An efficient synthesis of perfunctionalyzed 1,3-thiazoles 2a-2b with good
yields has been carried out by a cyclocondensation reaction between the α-metallated
dimethyl N-(ethoxycarbonylmethyl)iminodithiocarbonate and aryl or alkylisothiocyanates.

In this paper we give account of an efficient synthesis of 5-aryl (or alkyl)amino-4-ethoxycarbonyl-
2-methylthio-1,3-thiazoles 2a-2f. These perfunctionalyzed 1,3-thiazoles can be used as
building blocks to obtain other heterocyclic structural complex systems by a convergent connection
with specific synthons. Thus, the methylthio on C2 can be substituted by halogen, O-, N-, and C-
nucleophiles by or without a previous oxidation of the sulfide. This strategy can be used, for
instance, to obtain the famotidine, an interesting antiulcer agent. By other hand, the
ethoxycarbonyl on C4 can be the starting point for a new heterocyclization to azadaryl compounds
that can be used as target molecules to obtain compounds of biological interest. Additionally,
the presence of the amine substituent on C5 can make possible the fusion of other hetero- or
homocycles of variable topology with 1,3-thiazole moiety.

We have previously reported that the dimethyl N-(ethoxycarbonylmethyl)iminodithiocarbonate (EMIC),
I, is an useful synthetic equivalent of the EtO$_2$C-C4-N=C2-SMe synthon that is a structural
unit present into 1,3-thiazoles whose substituents on C5 position come from an unsaturated
electrophile. Thus, 5-alkylthio-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles have been obtained by
a cyclocondensation reaction of EMIC with carbon disulfide, and later alkylation of intermediate
1,3-thiazole-5-thiolate with alkyl halides.

We describe now an efficient synthesis of 5-aryl (or alkyl)amino-4-ethoxycarbonyl-2-methylthio-
1,3-thiazoles, 2a-2f, by a cyclocondensation reaction between the α-metallated EMIC and
aryl and alkyl isothiocyanates (Scheme I).

![Scheme 1](image-url)

R: a, Ph; b, p-FC$_6$H$_4$; c, p-MeC$_6$H$_4$; d, p-MeO$_2$C$_6$H$_4$; e, Et; f, n-Bu
Different base/solvent systems, base/EMIC proportions, and reaction conditions for metallation of 1, and condensation of α-metallated EMIC with phenyl isothiocyanate were tested. The results have been gathered in Table 1.

Table 1. Observed yields for 4-ethoxycarbonyl-2-methylthio-5-phenylamino-1,3-thiazole, 2a, from 1 and phenyl isothiocyanate.

<table>
<thead>
<tr>
<th>Run</th>
<th>Base/solvent</th>
<th>Base/EMIC/PhNCS</th>
<th>metallation</th>
<th>condensation</th>
<th>yield(%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KBr5O/THF</td>
<td>1.1/1/1</td>
<td>20°C/0.5 h</td>
<td>20°C/0.5 h</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>KBr5O/THF</td>
<td>1.1/1/1</td>
<td>-78°C/0.5 h</td>
<td>-78°C/0.5 h</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>KBr5O/THF</td>
<td>1.4/1/1</td>
<td>-78°C/0.5 h</td>
<td>-78°C/0.5 h</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>NaH/DMSO</td>
<td>1.5/1/1</td>
<td>20°C/2 h</td>
<td>b)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NaH/DME</td>
<td>1.5/1/1</td>
<td>0°C/0.5 h</td>
<td>20°C/0.5 h</td>
<td>c)</td>
</tr>
<tr>
<td>6</td>
<td>NaOAc</td>
<td>---/1/1</td>
<td>20°C/2 h</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

a) Isolated product. Except in the indicated cases none other product was detected by TLC except 1.
b) Bis(4-ethoxycarbonyl-2-methylthio-1-phenyl imidazolyl)disulfane was obtained (10%) by acidification to pH 5 of the reaction crude after of the extraction with diethyl ether at basic pH with negative result.7 c) Methyl N-phenylidithiocarbamate was obtained with a yield of 45%.d) The following conditions were used: CH2Cl2/NaOH-H2O (4%)/n-Bu4NBr.

In all cases, except runs 4 and 5, the 1,3-thiazole 2a was the unique isolated product. The best result in 2a was obtained with the KBr5O/THF system (Table 1, run 3). From run 4 a solid with a melting point of 200°C was isolated and identified as bis[5-(4-ethoxycarbonyl-2-methylthio-1-phenyl)imidazolyl]disulfane by according with IR, 1H- and 13C-nmr data.7 A related result has been described in the literature8 for the cyclocondensation reaction of N-tosylimethylisocyanide and isothiocyanates with the NaH/DMSO system.

From the results gathered in Table 1, the synthesis of 5-aryl(or alkyl)amino-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles, 2a-2f, was verified with an 40% excess of KBr5O, and m-deficient and m-excess aryl isothiocyanates, and alkyl isothiocyanates. The results have been collected in Table 2.

All new compounds have been fully characterized from their IR, 1H-nmr, 13C-nmr, and ms data together a satisfactory analytical data. The IR, 1H-, 13C-nmr, and ms key data have been gathered in Table 3.

The IR data support the presence of an amine and conjugated carbonyl groups. The single band at 3220-3420 cm⁻¹ can be assigned to a NH group,9 and the band at 1660-1730 cm⁻¹ to a carbonyl group of a conjugated ester with an unsaturated system (Ref. 9, p. 177).
Table 2. Observed yields by the synthesis of 5-aryl(or alkyl)amino-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles 2a-2f.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield(%)</th>
<th>Mp(°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>Ph</td>
<td>90</td>
<td>79-80b</td>
</tr>
<tr>
<td>2b</td>
<td>p-FC₆H₄</td>
<td>65</td>
<td>54-55c</td>
</tr>
<tr>
<td>2c</td>
<td>p-Me₆H₄</td>
<td>73</td>
<td>64-65b</td>
</tr>
<tr>
<td>2d</td>
<td>p-MeOC₆H₄</td>
<td>55</td>
<td>57-58b</td>
</tr>
<tr>
<td>2e</td>
<td>Et</td>
<td>59</td>
<td>liquidd</td>
</tr>
<tr>
<td>2f</td>
<td>n-Bu</td>
<td>77</td>
<td>liquidd</td>
</tr>
</tbody>
</table>

aYield in purified product. bRecrystallized from methanol. cRecrystallized from hexane. dPurified by silica gel flash chromatography.

Table 3. IR, ¹H-nmr, ¹³C-nmr, and Ms key data of 1,3-thiazoles 2a-2f.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR(cm⁻¹)</th>
<th>¹H-nmr</th>
<th>¹³C-nmr</th>
<th>Ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NH(s)</td>
<td>CO(s)</td>
<td>NH</td>
<td>SCH3</td>
</tr>
<tr>
<td>2a</td>
<td>3400</td>
<td>1660</td>
<td>9.80a</td>
<td>2.65</td>
</tr>
<tr>
<td>2b</td>
<td>3280</td>
<td>1690</td>
<td>9.58a</td>
<td>2.62</td>
</tr>
<tr>
<td>2c</td>
<td>3220</td>
<td>1730</td>
<td>9.60a</td>
<td>2.62</td>
</tr>
<tr>
<td>2d</td>
<td>3300</td>
<td>1700</td>
<td>9.47a</td>
<td>2.59</td>
</tr>
<tr>
<td>2e</td>
<td>3310</td>
<td>1710</td>
<td>7.40c</td>
<td>2.56</td>
</tr>
<tr>
<td>2f</td>
<td>3420</td>
<td>1700</td>
<td>7.27c</td>
<td>2.52</td>
</tr>
</tbody>
</table>

aBroadened singlet. bInterchangeable assignments. cBroadened triplet.

The ¹H-nmr data prove the presence of an ethyl ester, a methylthio, and a secondary amine groups. The signals observed at 2.52-2.65 ppm support the presence of a methylthio group bounded to a sp² carbon,¹⁰ and the signals at 9.47-9.80 ppm and 7.27-7.40 ppm an aromatic (2a-2d) or aliphatic (2e-2f) secondary amine groups (Ref. 10, p. 118).

The ¹³C-nmr data support the proposed structure to 2a-2f compounds. The assignment of signals to C2 and C4 carbons is proposed by comparison with the chemical shifts reported by us for C2 and C4 carbons of 5-aryl(or alkylthio)-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles (C2: 161.73-163.74 ppm; C4: 137.74-141.46 ppm).⁵

The Ms data are according to the proposed structure to 2a-2f 1,3-thiazoles. In all cases the base peak has been the molecular ion, and a common ion m/z:91 has been detected. This peak can be reasonably assigned to MeS-C≡S⁺ ion (Ref. 1, p. 244), and its formation precludes any other relative disposition of the sulfur heteroatoms in the molecular ion.

Thus, the synthesis of 1,3-thiazoles by this method has shown to be highly selective because four
different products can be originated taking into account the regioselectivities of condensation and cyclization steps (Scheme 2).

![Diagram of chemical reactions]

- Scheme 2 -

Although some related syntheses have been previously described—cyclocondensation reactions of nitrile ylides with monothioesters,\(^1\) \(O\)-metallated isocyanides with carbon disulfide,\(^8\) monothio,\(^9\) and dithioesters;\(^1\) EMIC with carbon disulfide,\(^5\) and rearrangement of mesoionic 1,3-oxazoles to mesoionic 1,3-thiazoles\(^1\)—none of these methods allows to obtain the perfunctionalized 1,3-thiazoles described in this paper.

**EXPERIMENTAL**

Melting points were determined in a Büchi 520 apparatus in capillary tubes and are uncorrected. The IR spectra were recorded on a Perkin Elmer 781 spectrometer. The \(^1\)H- and \(^1\)H-NMR spectra were recorded on a Varian FT 80A spectrometer (79.542 MHz for \(^1\)H and 20.00 MHz for \(^1\)C). Solutions in CDCl\(_3\) (13% and 25% w/v, respectively) at 303\(^\circ\)K were used. Chemical shifts are quoted in \(\delta\) values using TMS as internal reference. Mass spectra were recorded on a Varian Matt 711 spectrometer by electron impact technique (70 eV). All elemental analyses were satisfactory. Silica gel 60 F\(_{254}\) plates (Merck) were used for TLC, and silica gel 273-400 mesh (Merck) was used for conventional flash column chromatographies.
Synthesis of 1,3 was accomplished from ethyl ester glycine hydrochloride (Aldrich Chemie), carbon disulfide, and methyl iodide following the procedure described previously by us.\(^5\) α-Metallated 1 was condensed with phenyl isothiocyanate in different base/solvent systems and/or reaction conditions (Table 1). The isolation of products was performed following a general procedure with special features gathered in Table 1.

**General procedure.** To a stirred solution of KBr\(^4\)O (0.785 g, 7 mmol) in 50 ml dry THF (at -78°C under nitrogen) was added dropwise a solution of 1 (1 g, 5 mmol) in 4 ml dry THF. After 0.5 h. at -78°C, a solution of 5 mmol of isothiocyanate in 4 ml dry THF was slowly added. After 30 min. at -78°C, the mixture was allowed to stand at room temperature for 2 h., and was then quenched with water, and extracted with diethyl ether (4×30 ml). The combined ethereal extracts were dried on MgSO\(_4\) (12 h.), and evaporated. The product was isolated by precipitation with pentane and recrystallized (2a-2d), or from silica gel flash chromatography 2e: n-hexane/ethyl acetate: 90/10 v/v; 2f: n-hexane/ethyl acetate: 95/5 v/v.

4-Ethoxycarbonyl-2-methylthio-5-phenylamino-1,3-thiazole, 2a. (KBr pellet) 3400, 2910-2820, 1660, 1620, 1590, 1570, 1420, 1255, 1205, 790 cm\(^{-1}\). \(^1\)H-Nmr, δ(ppm): 1.42 (t, 3H, \(CH_3\)CH\(_2\), J=7.0 Hz), 2.62 (s, 3H, \(SCH_3\)), 4.41 (q, 2H, \(CH_2\)CH\(_3\), J=7.0 Hz), 7.05-7.53 (m, 5H, Ph), 9.80 (bs. 1H, NH). \(^13\)C-Nmr, δ(ppm): 14.56 (\(CH_3\)CH\(_2\)), 17.55 (\(SCH_3\)), 60.87 (\(CH_2\)CH\(_3\)), 116.61 (\(p\)-C), 122.90 (C5), 123.81 (o-C), 129.69 (m-C), 140.64 (C4), 155.79 (\(ipso\)-C), 164.72 (C2), 164.76 (CO\(_2\)Et). Ms (\(\%\)): 294 (9.4), 295 (14.3), 294 (100.0), 248 (37.1), 247 (3.7), 215 (77.1), 214 (19.4), 91 (19.7), 77 (15.1).

4-Ethoxycarbonyl-5-p-fluorophenylamino-2-methylthio-1,3-thiazole, 2b. (KBr pellet): 3280, 3100, 2990, 1690, 1670, 1600, 1580, 1470, 1230, 1200, 1190, 860, 780 cm\(^{-1}\). \(^1\)H-Nmr, δ(ppm): 1.43 (t, 3H, \(CH_3\)CH\(_2\), J=7.0 Hz), 2.62 (s, 3H, \(SCH_3\)), 4.41 (q, 2H, \(CH_2\)CH\(_3\), J=7.0 Hz), 6.81-7.34 (m, 4H, Ar), 9.58 (bs, 1H, NH). \(^13\)C-Nmr, δ(ppm): 14.53 (\(CH_3\)CH\(_2\)), 17.59 (\(SCH_3\)), 60.95 (\(CH_2\)CH\(_3\)), 116.48 (d, \(\alpha\)-C, 2J\(^{13}\)C,\(^{19}\)F)=22.6 Hz), 120.28 (d, \(\alpha\)-C, 3J\(^{13}\)C,\(^{19}\)F)=11.8 Hz), 122.60 (C5), 137.06 (d, \(ipso\)-C, 4J\(^{13}\)C,\(^{19}\)F)=2.6 Hz), 146.20 (C4), 156.89 (C2), 159.38 (d, \(\alpha\)-C, 2J\(^{13}\)C,\(^{19}\)F)=244.4 Hz), 164.69 (CO\(_2\)Et). Ms (\(\%\)): 314 (10.3), 313 (19.1), 312 (100.0), 266 (45.6), 265 (4.1), 233 (69.1), 232 (45.6), 95 (94.1), 91 (44.1).

4-Ethoxycarbonyl-5-p-methoxyphenylamino-2-methylthio-1,3-thiazole, 2c. (KBr pellet): 3220, 3000, 2900, 1730, 1660, 1590, 1580, 1420, 1270, 1200, 820, 780 cm\(^{-1}\). \(^1\)H-Nmr, δ(ppm): 1.42 (t, 3H, \(CH_3\)CH\(_2\), J=7.1 Hz), 2.32 (s, 3H, \(CH_3\)-Ar), 2.62 (s, 3H, \(SCH_3\)), 4.41 (q, 2H, \(CH_2\)CH\(_3\), J=7.1 Hz), 7.10 (m, 4H, Ar), 9.60 (bs, 1H, NH). \(^13\)C-Nmr, δ(ppm): 14.22 (\(CH_3\)CH\(_2\)), 17.32 (\(SCH_3\)), 20.46 (\(CH_3\)-Ar), 60.47 (\(CH_2\)CH\(_3\)), 118.38 (o-C), 122.15 (C5), 129.84 (\(p\)-C), 133.48 (\(ipso\)-C), 137.92 (m-C), 145.50 (C4), 156.44 (C2), 164.35 (CO\(_2\)Et). Ms (\(\%\)): 310 (9.2), 309 (14.9), 308 (100.0), 262 (48.6), 261 (8.1), 229 (64.5), 228 (16.7), 91 (13.2).
4-Ethoxycarbonyl-5-p-methoxyphenylamino-2-methylthio-1,3-thiazole, 2d. Ir (KBr pellet): 3300, 1660, 1550, 1460, 1180, 1170, 1150 cm⁻¹. 1H-Nmr, δ(ppm): 1.41 (t, 3H, CH₃CH₂, J=7.0 Hz), 2.59 (s, 3H, SCH₃), 3.78 (s, 3H, OCH₃), 4.42 (q, 2H, CH₂CH₃, J=7.0 Hz), 6.77-7.47 (m, 4H, Ar). 9.47 (bs, 1H, NH). 13C-Nmr, δ(ppm): 14.26 (CH₃CH₂), 17.37 (SCH₃), 55.19 (OCH₃), 60.44 (CH₂CH₃), 113.92 (ipso-C), 114.54 (m-C), 121.14 (o-C), 121.54 (C₅), 133.69 (C₄), 156.48 (p-C), 158.17 (C₂), 164.34 (CO₂Et). Ms (?): 326 (10.6), 305 (15.8), 259 (100.0), 278 (79.0), 277 (53.3), 245 (31.1), 244 (21.6), 91 (25.3).

4-Ethoxycarbonyl-5-ethylamino-2-methylthio-1,3-thiazol, 2e. Ir (film): 3310, 2980, 2860, 1710, 1660, 1550, 1390, 1220, 1150 cm⁻¹. 1H-Nmr, δ(ppm): 0.93 (t, 3H, CH₃CH₂NH, J=7.1 Hz), 1.35 (t, 3H, CH₃CH₂OCO, J=7.0 Hz), 2.56 (s, 3H, SCH₃), 3.11 (qd, 2H, CH₂CH₂NH, J=6.0 Hz), 4.27 (q, 2H, CH₂CH₂OCO, J=7.0 Hz), 7.40 (bt, 1H, NH, J=5.0 Hz). 13C-Nmr, δ(ppm): 13.39 (CH₂CH₂OCO, CH₃CH₂NH), 66.51 (SCH₃), 48.88 (CH₃CH₂NH), 58.85 (CH₂CH₂OCO), 117.57 (C₅), 142.50 (C₄), 161.03 (C₂), 162.96 (CO₂Et). Ms (?): 248 (8.3), 247 (9.2), 246 (100.0), 200 (20.2), 199 (3.5), 167 (25.1), 166 (22.1), 91 (15.0).

4-Ethoxycarbonyl-5-n-butylamino-2-methylthio-1,3-thiazole, 2f. Ir (film): 3420, 2900, 1700, 1660, 1550, 1460, 1420, 1200, 1150 cm⁻¹. 1H-Nmr, δ(ppm): 0.93 (t, 3H, CH₃(CH₂)₃, J=7.0 Hz), 1.35 (m, 4H, CH₃(CH₂)₂CH₂NH), 1.42 (t, 3H, CH₃CH₂OCO, J=7.1 Hz), 2.52 (s, 3H, SCH₃), 3.10 (m, 2H, CH₃(CH₂)₂CH₂NH), 4.27 (q, 2H, CH₂CH₂OCO, J=7.1 Hz), 7.27 (bt, 1H, NH, J=7.27 Hz). 13C-Nmr, δ(ppm): 12.87 (CH₃(CH₂)₃), 13.82 (CH₂CH₂OCO), 17.08 (SCH₃), 19.08 (CH₃CH₂(CH₂)₂), 30.51 (CH₃CH₂CH₂CH₂NH), 48.18 (CH₃(CH₂)₂CH₂NH), 59.40 (CH₃CH₂OCO), 118.33 (C₄), 143.02 (C₅), 162.73 (C₂), 163.73 (CO₂Et). Ms (?): 276 (8.7), 275 (10.1), 274 (100.0), 228 (35.3), 227 (4.1), 195 (40.1), 194 (8.3), 91 (12.0).

REFERENCES AND NOTES.


7. Spectroscopic data of bis(5-(4-ethoxycarbonyl-2-methylthio-1-phenylimidazolyldisulfane: IR (CHCl₃): 1700, 1540, 1520, 1400, 1220 cm⁻¹. ¹H-Nmr, δ(ppm): 1.38 (t, 3H, CH₃CH₂, J=7.12 Hz), 2.66 (s,3H, SCH₂), 4.29 (q, 2H, CH₂CH₃, J=7.12 Hz), 7.02-7.55 (m, 5H, Ph). ¹³C-Nmr, δ(ppm): 14.18 (CH₃CH₂), 14.49 (SCH₂), 60.68 (CH₂CH₃), 128.20, 128.53, 129.00, 129.56 (aromatic carbons), 133.98 (–CO–C=), 138.69 (–S=C=), 149.66 (–S=C= N), 161.33 (CO₂Et).


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