

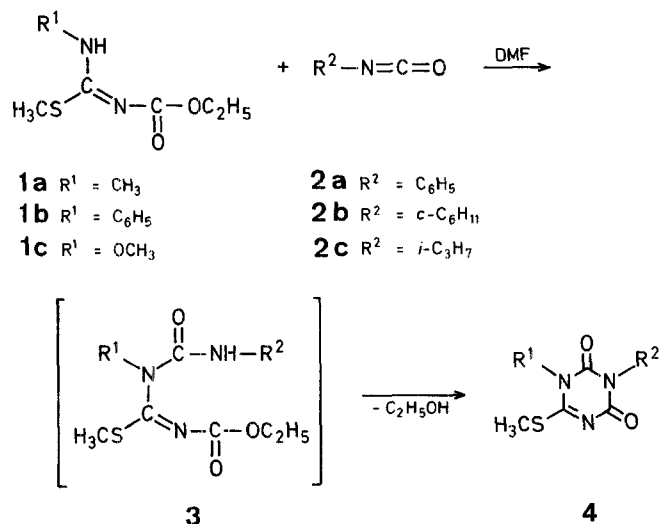
A Convenient One-Step Synthesis of 1,3-Disubstituted 6-Methylthio-2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazines [6-Methylthio-1,3,5-triazine-2,4(1*H*, 3*H*)-diones]

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The title compounds (**4**) are of interest from a phytotoxic standpoint¹ and one of them is a precursor of a potent herbicide (Hexazinone)². The hitherto reported syntheses of compounds **4** can be classified in two groups^{3,4}. One involves aminocarbonylation of *S*-methylisothiourea and subsequent cyclization followed by methylation. The other consists of the one-step cyclocondensation of *N*-substituted bis[chlorocarbonyl]-amines with *N*-substituted *S*-methylisothioureas. In our view, the former method is not satisfactory with respect to total yield and versatility. The latter is inconvenient in connection with the use of less accessible starting materials. We report here a convenient one-pot preparation of 1,3-disubstituted 6-methylthio-1,3,5-triazine-2,4(1*H*, 3*H*)-diones (**4**, 6-methylthio-2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazines) in good yields by reaction of *N*-substituted *N'*-ethoxycarbonyl-*S*-methylisothioureas (**1a**, **b**) with isocyanates (**2a**, **b**, **c**).

Appropriate *N*-substituted *N'*-ethoxycarbonyl-*S*-methylisothioureas⁵ (**1a**, **b**, **c**) were treated with excess phenyl isocyanate (1.5 equiv) in dimethylformamide at room temperature for 12 h; the *N*-substituted *S*-methylisothioureas **1a**, **b** were directly converted into the 1,3,5-triazinediones **4aa** and **4ba** in yields of 82–85%. Attempts to couple **1a**, **b** with excess alkyl isocyanates (2.0 equiv) under similar conditions were unsuccessful. However, on conducting the reaction in the presence of a basic catalyst (0.1 equiv) such as 1,1,3,3-tetramethylguanidine, products **4ab** and **4bd** respectively, were obtained in yields of 81–87%.



The structures of all products **4** were confirmed by microanalysis, I. R., and ¹H-N.M.R. spectra.

The reaction conditions are mild and the isolation procedures simple. In contrast, treatment of *N*-ethoxycarbonyl-*S*-methylisothiourea (**1c**) bearing an electron-withdrawing substituent with phenyl isocyanate leads to the formation of

Table. 1,6-Disubstituted 6-Methylthio-1,3,5-triazine-2,4(1*H*,3*H*)-diones (**4**) prepared

4	R ¹	R ²	Yield ^a [%]	m.p. ^b [°C]	Molecular Formula or m.p. [°C] reported	I. R. (KBr) $\nu_{C=O}$ [cm ⁻¹]	¹ H-N.M.R. (CDCl ₃ /TMS _{int}) ^c δ [ppm]
aa	CH ₃	C ₆ H ₅	85	240–241°	236–239° ⁴	1680; 1720	2.52 (s, 3H); 3.52 (s, 3H); 7.1–7.7 (m, 5H)
ba	C ₆ H ₅	C ₆ H ₅	82	230–231°	229–232° ⁴	1680; 1720	2.50 (s, 3H); 7.1–7.6 (m, 10H)
ab	CH ₃	<i>c</i> -C ₆ H ₁₁	81	141°	135–137° ²	1680; 1710	1.05–2.25 (m, 10H); 2.60 (s, 3H); 3.40 (s, 3H); 4.19–4.70 (m, 1H)
bc	C ₆ H ₅	<i>i</i> -C ₃ H ₇	87	109°	C ₁₃ H ₁₅ N ₃ O ₂ S ^d (277.3)	1670; 1720	1.50 (d, 6H); 2.48 (s, 3H); 4.8–5.4 (m, 1H); 7.1–7.7 (m, 5H)

^a Yield of pure isolated product (satisfactory microanalysis).^b Uncorrected.^c Recorded on a Hitachi R-900 spectrometer.^d calc. C 56.31 H 5.45 N 15.16
found 56.29 5.20 15.08

N-aminocarbonyl-*N'*-ethoxycarbonyl-*S*-methylisothiourea (**3ca**) in 58% yield instead of a cyclic product. Attempted cyclization of the intermediate **3ca** under basic conditions leads to cleavage into the starting materials in quantitative yield. The above described one-pot reaction may be characterized as a combination of the addition of isocyanates and simultaneous intramolecular cyclization to afford the 1,3,5-triazine ring system.

The *N*-substituted *N'*-ethoxycarbonyl-*S*-methylisothioureas **1a, b, c** (methyl *N*-substituted *N'*-ethoxycarbonylcarbamidodithioates) were prepared in 95–98% overall yields from ethoxycarbonyl isothiocyanate and amines and methylation of the resultant *N*-ethoxycarbonylthioureas⁵.

6-Methylthio-2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazines **4aa** and **4ba**; General Procedure:

To a solution of the *N*-ethoxycarbonyl-*S*-methylisothiourea (**1a, b**; 30 mmol) in dimethylformamide (20 ml), phenyl isocyanate (**2a**; 5.3 g, 45 mmol) is added. The mixture is stirred at room temperature for 12 h. The resultant solution is evaporated in vacuo to yield a syrup which is recrystallized from hexane/acetone to give the analytically pure compound **4aa** or **4ba**.

6-Methylthio-2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazines **4ab** and **4bc**; General Procedure:

To a solution of the *N*-ethoxycarbonyl-*S*-methylisothiourea (**1a, b**; 10 mmol) and 1,1,3,3-tetramethylguanidine (0.12 g, 1.0 mmol) in dimethylformamide (20 ml), the alkyl isocyanate (**2b, c**; 20 mmol) is added. The mixture is stirred at room temperature for 12 h. The resultant solution is evaporated in vacuo to yield a syrup which is crystallized from hexane/acetone to give the analytically pure compound **4ab** or **4bc**.

N-Ethoxycarbonyl-*N'*-methoxy-*N'*-phenylaminocarbonyl-*S*-methylisothiourea (**3ca**, Methyl *N*-Ethoxycarbonyl-*N'*-methoxy-*N'*-phenylaminocarbonylcarbamidodithioate):

To a solution of *N*-ethoxycarbonyl-*S*-methylisothiourea (**1c**; 1.9 g, 9.9 mmol) in dimethylformamide (10 ml), phenyl isocyanate (1.7 g, 14.8 mmol) is added. The mixture is heated at 70°C for 8 h. After cooling, the solution is evaporated in vacuo. The crude residue is purified by column chromatography on silica gel and the product eluted with hexane/acetone (10/1) to give the pure product **3ca**; yield: 1.8 g (58%); m.p. 109°C (isopropanol).

C₁₃H₁₇N₃O₄S calc. C 50.16 H 5.50 N 13.50
(311.3) found 50.14 5.67 13.65

I. R. (KBr): ν = 1760, 1650 cm⁻¹ (C=O).

¹H-N.M.R. (CDCl₃/TMS_{int}): δ = 1.30 (t, 3H); 2.15 (s, 3H); 3.90 (s, 3H); 4.25 (q, 2H); 6.9–7.6 ppm (m, 5H).

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¹ J. J. Fuchs, K. Lin, *German Patent (DBP)* 2326312 (1973), E. I. du Pont de Nemours; *C. A.* **80**, 59971 (1974).² 1-Methyl-3-cyclohexyl-6-dimethylamino-1,3,5-triazine-3,5-(1*H*, 3*H*)-dione (Hexazinone) was easily prepared by the reaction of 6-methylthio-1,3,5-triazine-3,5 (1*H*, 3*H*)-dione (**4ab**) with dimethylamine: K. Lin, *U.S. Patent* 3902887 (1975), E. I. du Pont de Nemours; *C. A.* **84**, 44169 (1976).³ M. Ogawa, T. Matsui, J. Tobitsuka, H. Kitamura, *Agric. Biol. Chem. (Japan)* **44**, 2161 (1980).⁴ H. G. Schlee, K. Sasse, L. Eue, *German Patent (DBP)* 2254200 (1974), Bayer A.G.; *C. A.* **81**, 37583 (1974).
G. Zumach, E. Kühle, *Synthesis* **1970**, 542.⁵ S. Y.-K. Tam, R. S. Klein, I. Wempen, J. J. Fox, *J. Org. Chem.* **44**, 4547 (1979).