Synthesis of 3-Aroyl-1-ethoxycarbonylmethyl-2-methylisothioureas and 2-Aroylimino-4-ethoxycarbonyl-hexahydropyrimidin-5-ones

Naoaki FUKADA*, Yoshikazu TAKAHASHI, Masahiro HAYASHI

Department of Chemistry, Faculty of Science, Chiba University, Yayoicho 1-33, Chiba 260, Japan

3-Aroyl-1-ethoxycarbonylmethyl-2-methylisothioureas and 2-aroylimino-4-ethoxycarbonyl-hexahydropyrimidin-5-ones were synthesized from dimethyl *N*-aroylcarbonimidodithioates and glycine ethyl ester.

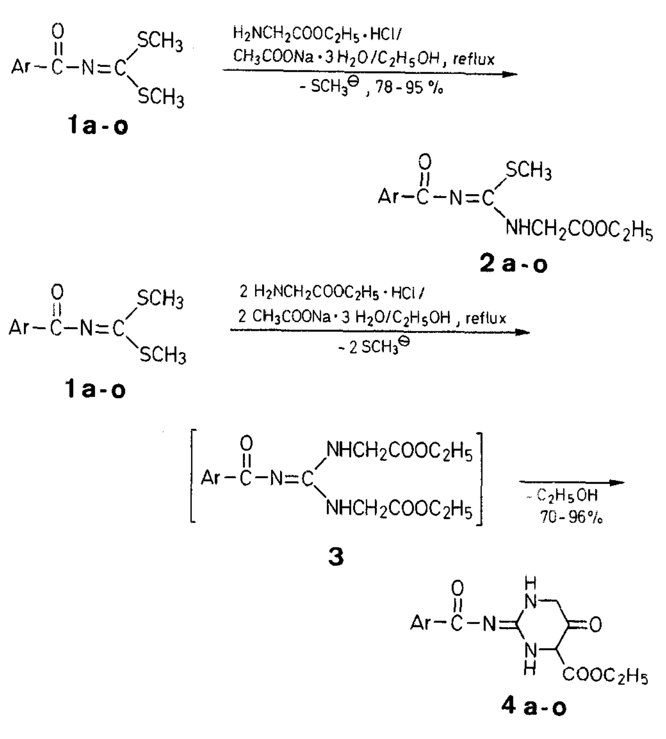
In a previous paper[1], we reported a general synthesis of dimethyl *N*-aroylcarbonimidodithioates **1** from aromatic amides, carbon disulfide, and sodium hydride. Esters **1** reacted with hydrazine hydrate on refluxing in ethanol to give 3-aryl-5-methylthio-1*H*-1,2,4-triazoles in good yields[1]. Augustin et al. reported the syntheses of dimethyl *N*-cinnamoyl- and *N*-aroylcarbonimidodithioates, and their reactions with nucleophilic compounds[2-5].

We report here a new synthesis of 3-aroyl-1-ethoxycarbonylmethyl-2-methylisothioureas **2** and 2-aroylimino-4-ethoxycarbonyl-hexahydropyrimidin-5-ones **4** from esters **1** and glycine ethyl ester. Equimolar mixtures of **1**, glycine ethyl ester hydrochloride, and sodium acetate were refluxed in ethanol to give monosubstituted compounds **2** in good yields (Table 1). Dimethyl *N*-(2-methoxybenzoyl)-carbonimidodithioate (**1e**) was more reactive and gave the disubstituted compound **4e** under the same conditions. Isothiourea **2e** was obtained from 10% excess of **1e** using double amounts of the solvent, followed by a few recrystallization.

Table 1. 3-Aroyl-1-ethoxycarbonylmethyl-2-methylisothioureas **2a**–**o**

Compound	Ar	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	I.R. (KBr) ν_{NH}	$\nu_{C=O}$ [cm^{-1}]	U.V. (C_2H_5OH) λ [nm] (log ε)	M.S. m/e (M^+)
2a	C_6H_5	84	97–98° (ethanol/hexane)	$C_{13}H_{16}N_2O_3S$ (280.3)	3130	1740, 1600	247 (4.10); 279 (4.30); 292 sh (4.18)	280
2b	2-H_3C—C_6H_4	78	59–61° (hexane)	$C_{14}H_{18}N_2O_3S$ (294.4)	3130	1754, 1738	251 (3.99); 279 (4.15)	294
2c	3-H_3C—C_6H_4	87	85–87° (ethanol)	$C_{14}H_{18}N_2O_3S$ (294.4)	3100	1742, 1598	253 (4.03); 282 (4.25)	294
2d	4-H_3C—C_6H_4	95	114–115° (ethanol)	$C_{14}H_{18}N_2O_3S$ (294.4)	3100	1740, 1596	257 (4.12); 284 (4.35); 292 sh (4.29)	294
2e	2-H_3CO—C_6H_4	86	107–108° (ethanol)	$C_{14}H_{18}N_2O_4S$ (310.4)	3110	1740, 1610	250 (4.06); 277 (4.17); 302 sh (3.93)	310
2f	4-H_3CO—C_6H_4	83	97–99° (ethanol)	$C_{14}H_{18}N_2O_4S$ (310.4)	3140	1742, 1598	222 (4.05); 285 sh (4.32); 296 (4.38)	310
2g	2-Cl—C_6H_4	85	72–74° (ethanol)	$C_{13}H_{15}ClN_2O_3S$ (314.8)	3140	1744, 1598	250 sh (3.99); 278 (4.20)	314
2h	4-Cl—C_6H_4	80	126–127° (ethanol)	$C_{13}H_{15}ClN_2O_3S$ (314.8)	3125	1740, 1600	255 (4.21); 280 sh (4.36); 284 (4.37); 291 sh (4.34)	314
2i	2-O_2N—C_6H_4	88	114–115° (ethanol/hexane)	$C_{13}H_{15}N_3O_5S$ (325.3)	3160	1750, 1596	262 (4.12)	325
2j	3-O_2N—C_6H_4	81	138–139° (ethanol/acetone)	$C_{13}H_{15}N_3O_5S$ (325.3)	3150	1742, 1598	228 (4.33); 283 (4.31)	325
2k	4-O_2N—C_6H_4	81	148° (ethanol)	$C_{13}H_{15}N_3O_5S$ (325.3)	3150	1732	241 (4.08); 275 sh (4.20); 296 (4.30)	325
2l	1-naphthyl	95	89–91° (ethanol)	$C_{17}H_{18}N_2O_3S$ (330.4)	3150	1744, 1600	217 (4.51); 242 (4.16); 273 sh (3.90); 312 (3.97)	330
2m	3-pyridyl	91	112–113° (ethanol/hexane)	$C_{12}H_{15}N_3O_3S$ (281.3)	3130	1742, 1600	232 (3.98); 286 (4.29)	281
2n	2-furyl	83	96–97° (ethanol)	$C_{11}H_{14}N_2O_4S$ (270.3)	3190	1756, 1610	258 sh (3.96); 266 (3.97); 298 (4.41)	270
2o	2-thienyl	90	95–96° (ethanol)	$C_{11}H_{14}N_2O_3S_2$ (286.4)	3100	1742	260 (4.07); 266 sh (4.02); 303 (4.24)	286

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.28, H ±0.11, N ±0.30).



On the other hand, the reaction of dimethyl *N*-(2-nitrobenzoyl)-carbonimidodithioate (**1i**) required twice the amount of glycine ethyl ester and three times the reaction time. These new compounds **2** are analogs of 3-cyano-1-ethoxycarbonylmethyl-2-methylisothiourea[6] or 3-ethoxycarbonylmethylamino-3-methylthio-1-phenyl-2-propen-1-one[7].

When two mol of glycine ethyl ester and sodium acetate were used, the reactions led to the diazine derivatives **4** (Table 2). Since nitro derivatives **1i–k** were less reactive, the reactions were carried out using excess of glycine ethyl ester in concentrated solution. The reaction appears to involve the intermediate **3**, which cyclizes with the elimination of ethanol to give **4**. The Dieckmann condensation reaction occurred under approximately neutral or rather acidic condition.

3-Aroyl-1-ethoxycarbonylmethyl-2-methylisothioureas 2a–o; General Procedure:

A mixture of ester **1** (0.001 mol)[1], glycine ethyl ester hydrochloride (0.14 g, 0.001 mol), sodium acetate (crystalline; 0.14 g, 0.001 mol), and ethanol (10 ml) is refluxed for 1 h. The solvent is evaporated and the residual solid or oil is kept in the refrigerator overnight. The solid is collected, washed with water (10 ml) to remove sodium chloride, dried, and recrystallized (Table 1). In the case of **2e**, 0.28 g

Table 2. 2-Aroylimino-4-ethoxycarbonyl-hexahydropyrimidin-5-ones **4a–o**

Compound	Ar	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	I.R. (KBr)		U.V. (C_2H_5OH)	M.S.
					ν_{NH}	$\nu_{C=O}$ [cm^{-1}]	λ [nm] (log ε)	m/e (M^+)
4a	C_6H_5	85	189–191° (ethanol)	$C_{14}H_{15}N_3O_4$ (289.3)	3330	1760, 1740 (sh), 1642	240 sh (4.10); 263 sh (4.37); 267 (4.39)	289
4b	2-H_3C—C_6H_4	79	117–118° (ethanol)	$C_{15}H_{17}N_3O_4$ (303.3)	3280	1760, 1740, 1640	227 sh (4.12); 266 (4.46)	303
4c	3-H_3C—C_6H_4	72	183–184° (ethanol acetone)	$C_{15}H_{17}N_3O_4$ (303.3)	3320	1756, 1740, 1640	234 sh (3.82); 269 (4.26)	303
4d	4-H_3C—C_6H_4	84	194° (ethanol acetone)	$C_{15}H_{17}N_3O_4$ (303.3)	3350	1768, 1742, 1640	233 sh (3.85); 270 (4.39)	303
4e	2-H_3CO—C_6H_4	96	150–152° (ethanol)	$C_{15}H_{17}N_3O_5$ (319.3)	3355	1768, 1742, 1628	213 (4.32); 265 (4.29); 305 (3.80)	319
4f	4-H_3CO—C_6H_4	73	190° (ethanol acetone)	$C_{15}H_{17}N_3O_5$ (319.3)	3355	1768, 1742, 1628	220 (4.25); 277 sh (4.41); 287 (4.46)	319
4g	2-Cl—C_6H_4	74	135–137° (ethanol)	$C_{14}H_{14}ClN_3O_4$ (323.7)	3280	1762, 1740, 1648	230 sh (4.15); 263 (4.33)	323
4h	4-Cl—C_6H_4	70	203° (ethanol acetone)	$C_{14}H_{14}ClN_3O_4$ (323.7)	3290	1758, 1740, 1640	235 sh (4.02); 271 (4.52); 280 sh (4.32); 287 sh (4.15)	323
4i	2-O_2N—C_6H_4	85	119–121° (ethanol)	$C_{14}H_{14}N_4O_6$ (334.3)	3350	1770, 1744, 1640	238 (4.36); 261 sh (4.30)	334
4j	3-O_2N—C_6H_4	75	190–191° (ethanol)	$C_{14}H_{14}N_4O_6$ (334.3)	3345	1760 (sh), 1750 1640	228 (4.45); 267 (4.46)	334
4k	4-O_2N—C_6H_4	74	223–224° (acetone)	$C_{14}H_{14}N_4O_6$ (334.3)	3330	1764, 1742, 1630	229 (4.12); 283 (4.21)	334
4l	1-naphthyl	90	100–102° (ethanol)	$C_{18}H_{17}N_3O_4$ (339.4)	3330	1760, 1740, 1640	217 (4.54); 237 sh (4.28); 259 sh (4.06); 310 (4.01)	339
4m	3-pyridyl	81	197–199° (ethanol)	$C_{13}H_{14}N_4O_4$ (290.3)	3350	1762, 1740, 1638	233 (4.16); 249 (3.87); 273 (4.34)	290
4n	2-furyl	70	182° (ethanol)	$C_{12}H_{13}N_3O_5$ (279.3)	3320	1750 (sh), 1742, 1638	228 (3.94); 287 (4.45)	279
4o	2-thienyl	76	204–205° (ethanol)	$C_{12}H_{13}N_3O_4S$ (295.3)	3330	1760 (sh), 1744, 1638	235 sh (3.89); 255 sh (4.02); 265 (4.07); 292 (4.28)	295

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.29, H ±0.11, N ±0.25).

(0.0011 mol) of **1e** and 20 ml of ethanol are used, and the resulting crude solid is recrystallized a few times. Trace amounts of the starting material **1e** or the product **4e** can be recognized in the I. R. spectra. In the case of **2i**, 0.28 g (0.002 mol) of glycine ethyl ester hydrochloride and 0.27 g (0.002 mol) of sodium acetate (crystalline) are used, and the reaction mixture is refluxed for 3 h.

2-Aroylimino-4-ethoxycarbonyl-hexahydropyrimidin-5-ones 4a–o; General Procedure:

A mixture of ester **1** (0.001 mol), glycine ethyl ester hydrochloride (0.28 g, 0.002 mol), sodium acetate (crystalline; 0.27 g, 0.002 mol), and ethanol (10 ml) is refluxed for 3 h. The reaction mixture is worked up as described for the preparation of **2** (Table 2). In the case of nitro derivative **4i**, 4j, or **4k**, 0.56 g (0.004 mol) of glycine ethyl ester hydrochloride, 0.54 g (0.004 mol) of sodium acetate (crystalline), and 7 ml of ethanol are used.

Received: October 24, 1985

---

[1] Sato, M., Fukada, N., Kurauchi, M., Takeshima, T. *Synthesis* **1981**, 554.
[2] Augustin, M., Richter, M., Salas, S. *J. Prakt. Chem.* **1980**, *322*, 55.
[3] Richter, M., Herrmann, C., Augustin, M. *J. Prakt. Chem.* **1980**, *322*, 434.
[4] Richter, M., Strauss, K., Schäder, H.-D., Augustin, M. *J. Prakt. Chem.* **1982**, *324*, 625.
[5] Richter, M., Strauss, K., Augustin, M. *Z. Chem.* **1982**, *22*, 103.
[6] Gante, J., Mohr, G. *Chem. Ber.* **1975**, *108*, 174.
[7] Rahman, A., Ila, H., Junjappa, H. *Synthesis* **1984**, 250.