Reaction of Benzoyl Isothiocyanate With Active Methylene Reagents: A Convenient Synthesis of Pyrazolo[5,4-*c*]pyrazole, 1,3-Oxazine, Thiazole and Pyrimidine Derivatives

R. M. Mohareb,* A. Habashi, N.S. Ibrahim, S. M. Sherif

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

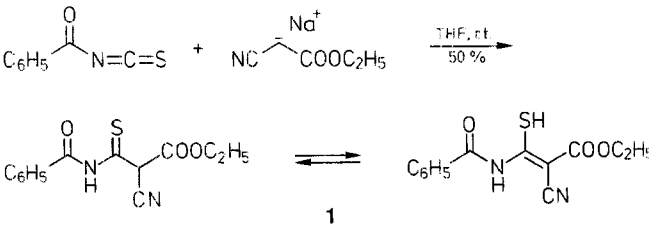
Benzoyl isothiocyanate reacts with active methylene reagents e.g. ethyl cyanoacetate, malonitrile and acetylacetone to give, in each case, the corresponding 1:1 adduct **1**, **13** and **14** respectively. Compound **1** was utilized for the synthesis of several heterocyclic derivatives. Compound **14** undergoes ready cyclization in basic medium to give the 1,3-oxazine derivative **15**. The structures of the products were assigned and confirmed on the basis of their elemental analysis and spectral data.

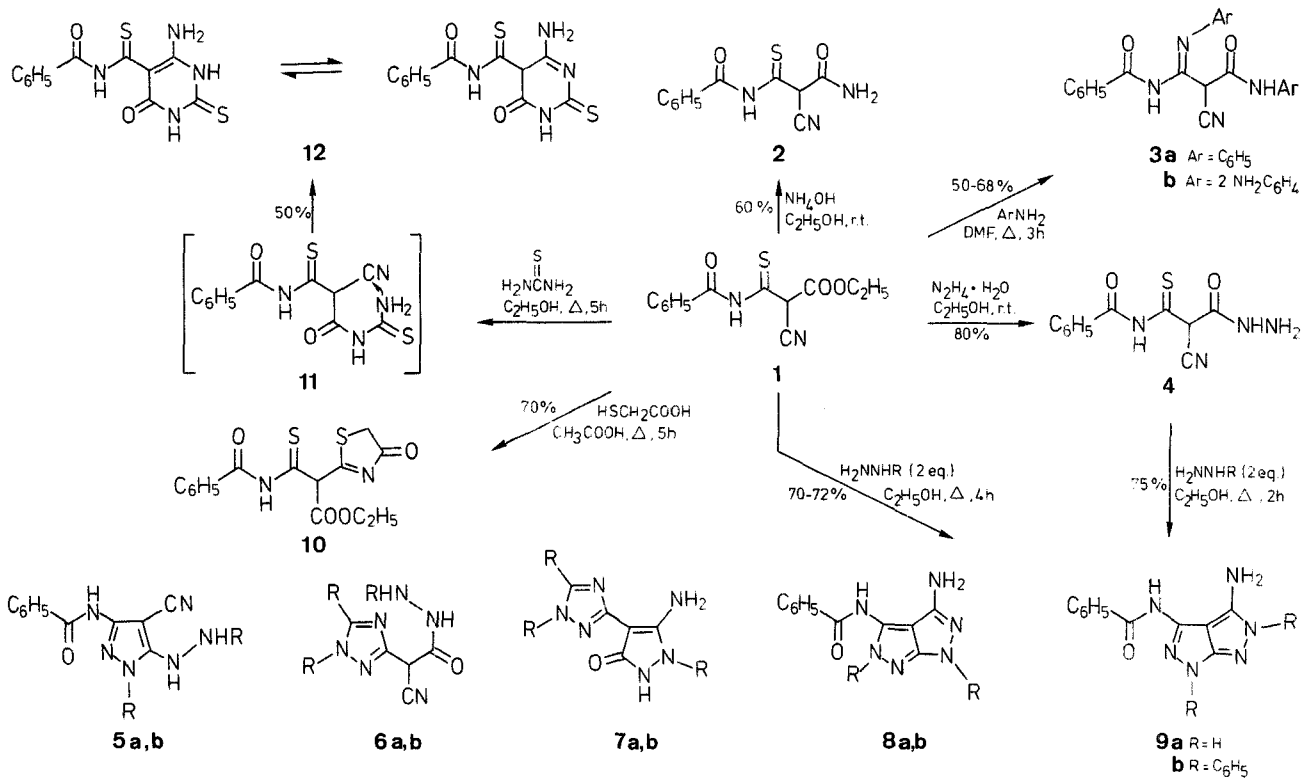
In previous publications, isothiocyanate derivatives were involved in reactions with amino and methylene functions of organic compounds.[1-10] However, the reaction of the title reagent with methylene function is still not as common as its reaction with amino function. In this article we report the reaction of benzoyl isothiocyanate with acidic methylene reagents and the utility of some of the reaction products in heterocyclic synthesis.

Benzoyl isothiocyanate reacts with the sodium salt of ethyl cyanoacetate to yield a 1:1 adduct (Table 1). Structure **1** was assigned for the reaction product based on IR and ^{1}H-NMR spectra (Table 2).

Further confirmation of structure **1** is obtained by studying the reactivity of the reaction product towards various chemical reagents. Thus, with aqueous ammonia at room temperature **1** forms the amide derivative **2**. The reaction of **1** with aniline or *o*-phenylenediamine in boiling dimethylformamide solution affords 3-arylamino-2-arylaminocarbonyl-3-benzoylamino propionitril derivatives **3a** and **3b**. The reaction was accompanied by the evolution of hydrogen sulfide (Scheme **A**).

Compound **1** reacts with hydrazines to give different products depending on the reaction conditions. Thus, with hydrazine





Scheme A

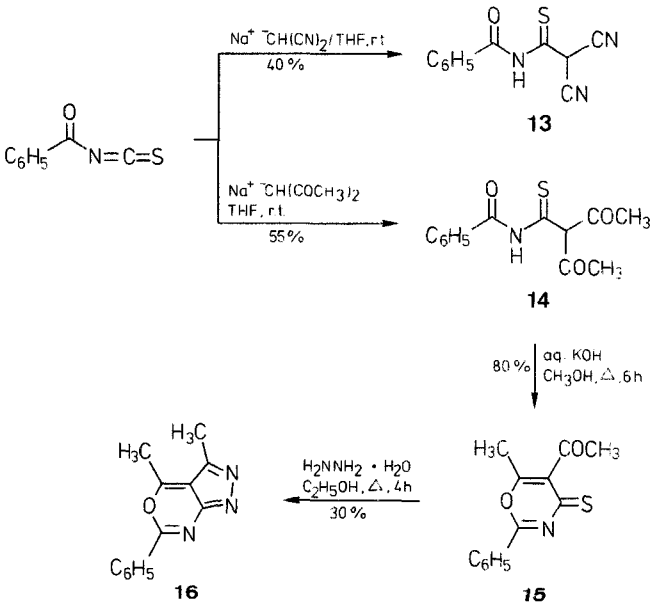
hydrate it reacts in the cold to give the hydrazide derivative **4**. On the other hand, **1** reacts with excess hydrazine hydrate and phenylhydrazine in boiling ethanol to give two products with molecular formulas $C_{11}H_{10}N_6O$ and $C_{23}H_{18}N_6O$, respectively (Table 1). Five possible isomeric structures **5a, b–9a, b** were considered for the reaction products (Scheme **A**). However, structures **5a, b** and **6a, b** were eliminated based on the absence of CN stretching band in the IR spectra of the reaction products. Structure **7a, b** was also eliminated based on ^{1}H-NMR spectra of the reaction products which revealed the presence of the phenyl protons of the benzamido group as a multiplet due to the anistorpic effect of the adjacent CO group. Among the other possibility of structures between **8a, b** or **9a, b** for the reaction products, structure **9a, b** seemed most likely. This was proved chemically, when **9a** was found to be identical (m.p and mixed m.p) with an authentic specimen prepared by boiling the acyclic hydrazide **4** with excess hydrazine hydrate in ethanol.

Compound **1** reacts with thioglycolic acid to give the thiazole derivative **10**. Formation of **10** finds parallel to the reaction reported in literature.[11] On the other hand, **1** reacts with thiourea to give the pyrimidine derivative **12**. Formation of **12** is

Table 1. Analytical data of compounds **1-4**, **9**, **10** and **12-16**

	Yield (%)	m.p. (°C) (Appearance)	Molecular Formula[a]
1	50	160 (white)	$C_{13}H_{12}N_2O_3S$ (276.2)
2	60	105 (yellow)	$C_{11}H_9N_3O_2S$ (247.2)
3a	68	143 (yellow) (382.2)	$C_{23}H_{18}N_4O_2$
3b	50	230–232 (brown)	$C_{23}H_{20}N_6O_2$ (412.2)
4	80	262–264 (white)	$C_{11}H_{10}N_4O_2S$ (270.2)
9a	72	180–183 (white)	$C_{11}H_{10}N_6O$ (242.1)
9b	70	132–133 (yellow)	$C_{23}H_{18}N_6O$ (394.2)
10	70	190–192 (yellow)	$C_{15}H_{14}N_2O_4S_2$ (350.3)
12	50	300 (white)	$C_{12}H_{10}N_4O_2S_2$ (314.2)
13	40	212 (organe)	$C_{11}H_7N_3OS$ (229.2)
14	55	170 (white)	$C_{13}H_{13}NO_3S$ (263.2)
15	80	192 (orange)	$C_{13}H_{11}NO_2S$ (245.2)
16	30	108–109 (yellow)	$C_{13}H_{11}N_3O$ (225.1)

[a] Satisfactory microanalyses obtained: C ±0.34, H ±0.34, N ±0.28, S ±0.30. Exception; **14**: H +0.47; **9b**: N ±0.41.



Scheme B

assumed to take place through intermediate formation of **11** (Scheme **A**).

Benzoyl isothiocyanate reacts also with malononitrile and acetylacetone to give 1:1 adducts **13** and **14**, respectively (Scheme **B**). Structures of compounds **13** and **14** were established based on analytical and spectral data (Tables 1 and 2).

Compound **14** undergoes readily cyclization in aqueous potassium hydroxide/methanol solution to give the 1,3-oxazine derivative **15**. Structure of **15** was established based on ^{1}H-NMR spectrum (Table 2). Compound **15** reacts with hydrazine hydrate to give the pyrazolo[3,4-*d*]oxazine derivative **16** (Scheme **B**).

All compounds obtained here were isolated in good yields and gave spectral data in agreement with their proposed structures (Tables 1 and 2). Further study for the reactivity of isothiocyanates towards active methylene reagents is now under consideration.

Table 2. Spectral Data of Compounds **1-4**, **9**, **10** and **12-16**

Product No.	IR (KBR) ν (cm^{-1})	^{1}H-NMR (DMSO) δ (ppm)
1	3450–3300 (NH); 3050 (arom CH); 2980, 2895 (CH_2, CH_3); 2220 (CN); 1710, 1680 (C=O)	1.78 (t, 3H, J = 8.0 Hz, CH_3); 4.21 (q, 2H, J = 6.3 Hz, CH_2); 4.89 (s, 1H, CH); 7.35 (m, 5H, C_6H_5)
2	3450–3300 (NH_2, NH); 3050 (arom CH); 2980 (CH_3); 2220 (CN); 1680 (C=O); 1630[a]	4.48 (s, 2H, NH_2); 5.0 (s, 1H, CH); 7.35 (m, 5H, C_6H_5); 10.1 (br s, 1H, NH)
3a	3470–3400 (NH); 3050 (arom CH); 2995 (CH); 2215 (CN); 1680–1695 (C=O)	5.11 (s, 1H, CH); 7.35–7.40 (m, 15H, $3C_6H_5$); 9.98–10.11 (s, 2H, 2NH)
3b	3450–3330 (NH_2, NH); 3050 (arom CH); 2990 (CH); 2215 (CN); 1695, 1690 (C=O); 1635[a]	–[b]
4	3460–3330 (NH_2, NH); 3060 (arom CH); 2990 (CH); 2220 (CN); 1680, 1670 (C=O); 1630[a], 1200 (C=S)	4.98 (s, 1H, CH); 5.21 (s, 2H, NH_2); 7.40 (m, 5H, C_6H_5); 9.90–10.01 (2 br s, 2H, 2NH)
9a	3450–3300 (NH_2, NH); 3050 (arom CH); 1685 (C=O); 1635[a]	4.56 (s, 2H, NH_2); 7.40 (m, 5H, C_6H_5); 8.78–9.0, 10.2 (2m, 3H, 3NH)
9b	3450–3300 (NH_2, NH); 3060 (arom CH); 1680 (C=O); 1650–1630 (C=C)[a]	4.89 (s, 2H, NH_2); 7.38 (m, 5H, C_6H_5); 10.0 (br s, 1H, NH)
10	3560–3320 (NH); 3060 (arom CH); 2990–2895 (CH, CH_2, CH_3); 1710, 1680 (C=O); 1650 (C=C); 1210 (C=S)	1.68 (t, 3H, J = 8.1 Hz, CH_3); 4.21 (q, 2H, J = 6.2 Hz, CH_2); 5.01 (s, 1H, CH); 6.89 (s, 2H, thiazole CH_2); 7.38 (m, 5H, C_6H_5); 10.21 (br s, 1H, NH)
12	3450–3300 (NH_2, NH); 3050 (arom CH + Pyrimidine CH); 1695, 1680 (C=O); 1630[a], 1200–1190 (C=S)	–[b]
13	3400–3250 (NH); 3050 (arom CH); 2995 (CH); 2220, 2210 (CN); 1200 (C=S)	6.0 (s, 1H, CH); 7.39 (m, 5H, C_6H_5); 9.89 (br s, 1H, NH)
14	3400–3350 (NH); 3060 (arom CH); 2990 (CH, CH_3); 1710, 1685 (C=O); 1190 (C=S)	1.70 (s, 6H, $2CH_3$); 6.01 (s, 1H, CH); 7.37 (m, 5H, C_6H_5); 10.21 (br s, 1H, NH)
15	3060 (arom CH); 2890 ($2CH_3$); 1720 (C=O); 1630 (C=C); 1190 (C=S)	1.12–1.78 (2s, 6H, $2CH_3$); 7.35–7.61 (m, 5H, C_6H_5)
16	3080 (arom CH); 2895 ($2CH_3$); 1639 (C=C, C=N)	1.61, 1.70 (2s, 6H, $2CH_3$); 7.35–7.59 (m, 5H, C_6H_5)

[a] δ_{NH_2}.
[b] Insoluble in commonly used ^{1}H-NMR solvents.

All melting points are uncorrected. Analytical data were obtained from the Microanalytical Data Unit at Cairo University. The IR spectra were obtained on a Pye-Unicam SP-1000 spectrophotometer. The ^{1}H-NMR spectra were recorded on a Varian A-90 Spectrometer.

3-Benzoylamino-2-cyano-3-thioxopropionicacid Ethyl Ester (1):
To a suspension of the sodium salt of ethyl cyanoacetate (0.1 mol) [prepared by adding 2.3 g sodium metal to a solution of ehtyl cyanoacetate (11.3 g, 0.01 mol) in tetrahydrofuran (50 ml)], benzoyl isothiocyanate [prepared by adding 7.8 g (0.01 mol) of ammonium thiocyanate to benzoyl chloride (14 g, 0.1 mol) in tetrahydrofuran (30 ml)] is added and the whole mixture is left at room temperature overnight. The yellow gel product obtained is diluted with water (20 ml) containing concentrated hydrochloric acid (2 ml). The oily material separated is then extracted by ethyl acetate (3 × 60 ml). After evaporation of the solvent *in vacuo*, the solid product so formed is isolated by suction and recrystallized from ethyl acetate; yield: 18.6 g (50%).

3-Benzoylamino-2-cyano-3-thioxopropionamide (2):
To a solution of **1** (2.7 g, 0.01 mol) in ethanol (20 ml) ammonium hydroxide (40 ml) is added. The whole mixture is left overnight at room temperature. The solid product formed on evaporation is collected by filtration and recrystallized from ethanol; yield: 1.3 g (60%).

3-Benzoylamino-2-cyano-3-phenyliminocarbonylpropionanilide (3a):
To a solution of **1** (2.7 g, 0.01 mol) in dimethylformamide (20 ml) aniline (2 g, 0.02 mol) is added. The whole mixture is heated under reflux for 3 h and then evaporated *in vacuo*. The remaining product is triturated with water containing few drops of concentrated hydrochloric acid, then collected by filtration and recrystallized from ethanol; yield: 2.5 g (68%).

(2-Aminophenyl)iminocarbonyl-3-Benzoylamino-2-cyanopropion-2-aminoacetanilide 3b):
The same experimental procedure described for synthesis of **3a** is carried out except using 2-amino aniline instead of aniline. The separated solid product is recrystallized from ethanol; yield: 2.6 g (50%).

3-Benzoylamino-2-cyano-3-thioxopropionhydrazide (4):
To a solution of **1** (2.7 g, 0.01 mol) in ethanol (30 ml) hydrazine hydrate (0.5 g, 0.01 mol) is added. The solid product, so precipitated, is collected by filtration and recrystallized from ethanol; yield: 2.1 g (80%).

4-Amino-3-benzoylamino-1,5-dihydro-pyrazolo[3,4-*c*]pyrazole derivatives (9a, b)
To a solution of **1** (2.7 g, 0.01 mol) in ethanol (30 ml) hydrazine hydrate (1 g, 0.02 mol) or phenyl hydrazine (2.1 g, 0.02 mol) is added. The whole mixture is heated under reflux for 4 h, then poured into ice containing concentrated hydrochloric acid (5 drops). The solid product formed, is collected by filtration. **9a** is recrystallized from dioxan; yield: 1.7 g (72%) and **9b** is recrystallized from dioxan; yield: 2.7 g (70%).

Compound **9a** is also prepared as follows: To a suspension of the hydrazide **4** (2.7 g, 0.01 mol) in ethanol (30 ml) hydrazine hydrate (1 g, 0.02 mol) is added. The whole mixture is heated under reflux for 2 h, then poured into ice containing concentrated hydrochloric acid (5 drops). The precipitated solid product is collected by filtration and crystallized from dioxan; yield: 1.8 g (75%).

2(2-Benzoylamino-1-ethoxycarbonyl-2-thioxo-ethyl)-4-oxo-4,5-dihydrothiazole (10):
To a solution of **1** (2.7 g, 0.01 mol) in glacial acetic acid (40 ml) thioglycolic acid (0.9 ml, 0.01 mol) is added. The mixture is heated under reflux for 5 h, then evaporated *in vacuo*. The remaining product is triturated with ethanol, then collected by filtration and recrystallized from acetic acid; yield: 2.3 g (70%).

4-Amino-5-(benzoylamino-thiocarbonyl)-6-oxo-2-thioxo-1,2,3,6-tetrahydropyrimidine (12):
To a suspension of **1** (2.7 g, 0.01 mol) in sodium ethoxide, prepared by dissolving sodium metal (0.23 g, 0.01 mol) in ethanol (40 ml), thiourea (0.8 g, 0.01 mol) is added. The mixture is heated under reflux for 5 h and then left to cool. The reaction product is poured into ice/water, then acidified with concentrated hydrochloric acid till pH 6. The solid product formed is collected by filtration and recrystallized from dimethylformamide; yield: 1.5 g (50%).

Benzoylamino-thiocarbonyl malodinitrile (13):
The same experimental procedure described for synthesis of **1** is carried out except using malononitrile instead of ethyl cyanoacetate. The product collected is recrystallized from ethyl acetate; yield: 9.2 g (40%).

3-Benzoylamino-thiocarbonyl-2,4-dioxopentane (14):
The same experimental procedure described for synthesis of **1** is carried out except using of acetylacetone instead of ethyl cyanoacetate. The product obtained is recrystallized from ethyl acetate; yield: 14.4 g (55%).

5-Acetyl-6-methyl-2-phenyl-4-thioxo-1,3-(4*H*)oxazine (15):
To a solution of **14** in methanol (50 ml) aqueous potassium hydroxide (5%, 20 ml) is added. The mixture is heated in a boiling water bath for 6 h, then poured into water (80 ml) and neutralised with concentrated hydrochloric acid till pH 7. The precipitated product, on standing for 4 h, is collected by filtration and recrystallized from dioxan; yield: 1.9 g (80%).

Pyrazolo[3,4-*d*]oxazine derivative (16):
To a solution of **15** (2.4 g, 0.01 mol) in ethanol (50 ml) hydrazine hydrate (0.5 ml, 0.01 mol) is added. The mixture is heated under reflux for 4 h (till the odour of hydrogen sulfide dissappears). The solid product is precipitated on adding water containing concentrated hydrochloric acid (0.2 ml), then collected by filtration and recrystallized from dimethylformamide; yield: 0.7 g (30%).

Received: 21 April 1986
(Revised form: 15 August 1986)

(1) Worrall, D.E. *J. Am. Chem. Soc.* **1920**, *42*, 1055.
(2) Worrall, D.E. *J. Am. Chem. Soc.* **1922**, *44*, 1551.
(3) Worrall, D.E. *J. Am. Chem. Soc.* **1924**, *46*, 2832.
(4) Worrall, D.E. *J. Am. Chem. Soc.* **1928**, *50*, 1456.
(5) Dehne, H., Krey, P. *Z. Chem.* **1979**, *19*, 211 and references cited therein.
(6) Fahmy, S.M., Mohareb, R.M. *Synthesis* **1983**, 478.
(7) Fahmy, S.M., Mohareb, R.M. *Tetrahedron* **1986**, *42*, 687.
(8) Elnagdi, M.H., Fahmy, S.M., Elmoghayar, M.R.H., Kandeel E.M. *J. Heterocycl. Chem.* **1979**, *16*, 61.
(9) Fahmy, S.M., Ibraheim, M.K.A., Abouhadid, K., Elnagdi, M.H. *Arch. Pharm.* **1982**, *315*, 791.
(10) Koren, B., Stanovik, B., Tisler, M. *J. Heterocycl. Chem.* **1977**, 621.
(11) Elnagdi, M.H., Elmoghayar, M.R.H., Hammam, A.G., Khallaf, S.A. *J. Heterocycl. Chem.* **1979**, *16*, 1541.