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Reactions of Thiocarbamoylaminophosphonium Salts obtained from Amines and the Combined Reagent, Triphenylphosphine–Thiocyanogen (TPPT): Preparation of Thioureas, Acylthioureas and Amides

Yasumitsu Tamura, Tomomi Kawasaki, Masahiro Adachi, and Yasuyuki Kita

Faculty of Pharmaceutical Sciences, Osaka University[1]

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The thiocarbamoylaminophosphonium salt (3) obtained from an amine (1) and TPPT (2) has been shown to be a useful synthetic intermediate for the preparation of thioureas (4), amides (10) and acylthioureas (11) by treatment with water and a carboxylic acid (9). The reaction mechanism is discussed.

Keywords——thiocarbamoylaminophosphonium salts; combined reagent of triphenylphosphine and thiocyanogen; 1,1-disubstituted thioureas; phosphinimine; acylthioureas; amides

We have briefly communicated a general useful synthetic method for 1,1-disubstituted thioureas (**4**)[2] and 2(1H)-quinazolinethiones (**7**)[3] by using the combined reagent, $Ph_3P(SCN)_2$ (TPPT) (**2**).[4] The formation of the thiocarbamoylaminophosphonium salts (**3** and **6**) was postulated in both reactions; the salts cannot be isolated but appear to be intermediates on the pathway to the products (**4** and **7**). The current work has centered on extending the scope of the reactions of the thiocarbamoylaminophosphonium salt (**3**) and we now report some transformations of **3** into amides (**10**) and acylthioureas (**11**) by treatment with carboxylic acids (**9**). The present paper describes these interesting reactions of **3**, including a full account of the work mentioned in a previous preliminary communication.[2]

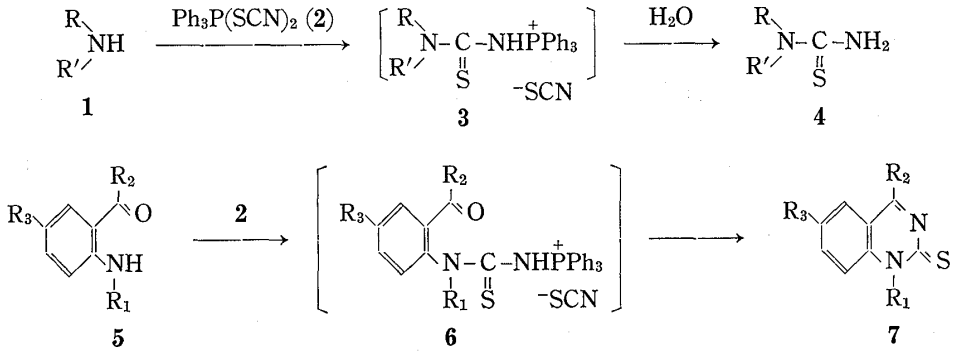

Chart 1

Treatment of an amine (**1**) with TPPT (**2**) in dry acetonitrile-methylene chloride at −40° for 2 hrs then at room temperature for several hrs followed by work-up of the initially formed phosphonium salt (**3**) with aqueous acetonitrile gave a good yield of the corresponding 1,1-disubstituted thiourea (**4**). The results are summarized in Table I. The presence of the phosphonium salt (**3**) as an intermediate is suggested by the following evidence: i) isolation

1) Location: *Yamada-kami, Suita, Osaka.*
2) Y. Tamura, M. Adachi, T. Kawasaki, and Y. Kita, *Tetrahedron Lett.*, **1978**, 1753.
3) Y. Tamura, T. Kawasaki, M. Tanio, and Y. Kita, *Synthesis*, **1979**, 120.
4) Y. Tamura, T. Kawasaki, M. Adachi, M. Tanio, and Y. Kita, *Tetrahedron Lett.*, **1977**, 4417.

TABLE I. Yields, Physical and Spectral Data for 1,1-Disubstituted Thioureas (**4a**—**g**)

No.	R	R′	Yield (%)	mp (from)	Lit. mp	IR ν_{max}^{tablet} (cm^{-1})	NMR δ ($CDCl_3$)
4a	CH_3	$CH_2C_6H_5$	65	147—149° (EtOH)	147.5—148.5° [a]	3425, 3270, 3170 1610, 1520, 1365	7.3 (5H, m, ArH) 5.9 (2H, bs, $-NH_2$) 5.0 (2H, s, $-CH_2N$) 3.15 (3H, s, NCH_3)
4b	CH_3	C_6H_5	80	103—104° (ligroin)	105—106° [b]	3420, 3250, 3150 1605, 1370	7.6—7.2 (5H, m, ArH) 5.9 (2H, bs, $-NH_2$) 3.7 (3H, s, NCH_3)
4c	C_2H_5	C_6H_5	50	111—112° (C_6H_6–*n*·hexane)	113° [c]	3370, 3260, 3155 1620, 1385	7.55—7.1 (5H, m, ArH) 5.8 (2H, bs, $-NH_2$) 4.2 (2H, q, $C\underline{H}_2CH_3$) 1.25 (3H, t, $CH_2C\underline{H}_3$)
4d	$-(CH_2)_5-$		70	125—127° (C_6H_6–*n*·hexane)	128° [b]	3330, 3175, 1640 1500, 1365	5.9 (2H, bs, NH_2) 3.9—3.6 (4H, m, $NCH_2\times2$) 1.8—1.5 (6H, m, $CH_2\times3$)
4e	$-(CH_2)_4-$		77	192—194° (ligroin)	197—199° [b]	3330, 3280, 3165 1625, 1510, 1370	5.65 (2H, bs, NH_2) 4.0—3.3 (4H, m, $NCH_2\times2$) 2.2—1.9 (4H, m, $CH_2\times2$)
4f	C_2H_5	C_2H_5	70	100—101° (iso-C_3H_7OH)	101—102° [b]	3365, 3275, 3175 1620, 1515, 1360	5.9 (2H, bs, $-NH_2$) 3.65 (4H, q, $C\underline{H}_2CH_3\times2$) 1.25 (6H, t, $CH_2C\underline{H}_3\times2$)
4g	CH_3	cyclo-C_6H_{11}	70	109—110° (iso-C_3H_7OH)	——	3380, 3315, 3200 1640, 1505, 1360	5.95 (2H, bs, NH_2) 5.1—4.5 (1H, m, N–CH<) 2.97 (3H, s, NCH_3) 2.0—1.0 (10H, m, $CH_2\times5$)

a) W.G. Finnegan, R.A. Henry and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).
b) H. Hartmann and I. Reuther, *J. Prakt. Chem.*, **315**, 144 (1973).
c) W. Gebhardt, *Chem. Ber.*, **17**, 2088 (1884).

of the phosphinimine (**8**) on treatment of (**3a**) obtained *in situ* from N-methylbenzylamine (**1a**) and TPPT (**2**) with an excess of **1a**, and ii) smooth conversion of **8** into **4a** on treatment with thiocyanic acid. Instead of aqueous work-up, the carboxylic acid (**9**) was allowed to react with the phosphonium salt (**3**) to give an amide (**10**) and/or acylthiourea (**11**) in various ratios depending on the species of **1** and **9** used.

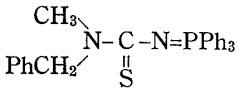

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Fig. 1

For instance, the phosphonium salt (**3a**) obtained from **1a** and **2** was allowed to react with phenylacetic acid (**9a**) at room temperature overnight to give the amide (**10a**) and acylthiourea (**11a**) in 19% and 28% yields, respectively, together with a 10% yield of the thiourea (**4a**). These structures (**10a** and **11a**) were determined from elemental, mass (MS) [**10a**; *m/e* 239 (M^+), **11a**; *m/e* 298 (M^+)], nuclear magnetic resonance (NMR) and infrared (IR) spectral data. Similarly, the phosphonium salt (**3**) obtained from N-methylbenzylamine or N-substituted and unsubstituted anilines with TPPT (**2**) was reacted with a variety of carboxylic acids (**9**) to give the corresponding amide (**10**) and/or acylthiourea (**11**). The results are summarized in Tables II and III. Furthermore, the phosphinimine (**8**) instead of **3a** reacted with **9** to afford a similar result: treatment of **8** with **9a** in methylene chloride at room temperature for 2 days gave (**10a**) and (**11a**) in 30% and 23% yields, respectively, together with an 18% yield of **4a**.

The formation of these products may be understood in terms of attack of a carboxylic acid (**9**) on the phosphorus atom of the phosphonium salt (**3**), leading to **12** followed by

TABLE II. Yields and Physical Data for (**10a—j**) and (**11a—j**)

	Amines (1) R	Amines (1) R′	Carboxylic acids (9) R″	Products: R(R′)NCOR″ (10) Yield (%)	mp (from) or bp	Lit.	Products: R(R′)NC(=S)NHCOR″ (11) Yield (%)	mp (from)	Lit.
a	$C_6H_5CH_2$	CH_3	$C_6H_5CH_2$	19	161 —165°/0.1 mmHg (bath temp.)	175 —176°/1.0 mmHg[a]	28	98.5—100° (*n*·hexane)	
b	$C_6H_5CH_2$	CH_3	cyclo-C_6H_{11}	—			31	131 —132° (C_6H_6–*n*·hexane)	
c	C_6H_5	H	CH_3	72	111.5—113° (AcOEt–*n*·hexane)	114 —116°[b]	—		
d	C_6H_5	H	*n*·C_5H_{11}	45	96 — 97° (AcOEt–*n*·hexane)	97.5— 98°[c]	13	68.5—69.5° (*n*·hexane)	71— 72°[b]
e	C_6H_5	H	$C_6H_5CH_2$	62	115 —116° (AcOEt–*n*·hexane)	118 —119°[c]	21	106 —108° (*n*·hexane)	107—108°[d]
f	C_6H_5	H	cyclo-C_6H_{11}	16	142 —143° (AcOEt–*n*·hexane)	146.5—147.5°[e]	45	160 —160.5° (*n*·hexane)	
g	C_6H_5	H	C_6H_5	—			42	143.5—145° (C_6H_6)	148—149°[b]
h	C_6H_5	CH_3	$C_6H_5CH_2$	8	151 —155°/0.1 mmHg (bath temp.)	141 —144°/0.3 mmHg[f] 121°/0.001 mmHg[g]	89	74 — 76° (AcOEt–*n*·hexane)	
i	C_6H_5	C_2H_5	$C_6H_5CH_2$	—			83	109 —110.5° (AcOEt–*n*·hexane)	
j	C_6H_5	*sec*–C_4H_9	$C_6H_5CH_2$	—			75	99.5—101° (AcOEt–*n*·hexane)	

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c) S. Yamada, Y. Kasai and T. Shioiri, *Tetrahedron Lett.*, **1973**, 1595.
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g) F. Weygand and H.J. Bestmann, *Chem. Ber.*, **92**, 528 (1959).

TABLE III. Spectral and Analytical Data for (**10a—j**) and (**11a—j**)

Compd. No.	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	NMR δ ($CDCl_3$)	Analysis (%) Calcd. (Found) C	H	N
10a	1630, 1600, 1495, 1450	7.17 (10H, s, ArH); 4.49 (2H, s, NC$\underline{H}_2$Ph); 3.62 (2H, s, COC$\underline{H}_2$Ph); 2.80 (3H, s, NCH_3)			
10c	3270, 1655, 1590, 1550, 1430	8.5 (1H, bs, NH); 7.7—6.8 (5H, m, ArH); 2.09 (3H, s, $COCH_3$)			
10d	3410, 1675, 1600, 1520, 1440	7.85 (1H, bs, NH); 7.7—6.9 (5H, m, ArH); 2.5—0.65 (11H, m, n-C_5H_{11})			
10e	3390, 1670, 1600, 1500, 1440	7.5—7.0 (11H, m, NH and ArH); 3.73 (2H, s, COC$\underline{H}_2$-Ph)			
10f	3410, 1670, 1590, 1510, 1430	7.7—6.9 (6H, m, NH and ArH); 2.5—1.0 (11H, m, cyclo-C_6H_{11})			
10h	1640, 1595, 1500, 1390	7.6—6.9 (10H, m, ArH); 3.44 (2H, s, COC$\underline{H}_2$Ph); 3.23 (3H, s, NCH_3)			
11a	3350, 1700, 1535, 1455, 1430, 1390	8.83 (1H, bs, NH); 7.28 (10H, s, ArH); 5.15 (2H, bs, NC$\underline{H}_2$Ph); 3.68 (2H, s, $COCH_2$Ph); 3.00 (3H, bs, NCH_3)	68.44 (68.25	6.08 6.08	9.39 9.53)
11b	3385, 1710, 1540, 1450, 1430, 1390	9.07 (1H, bs, NH); 7.32 (5H, s, ArH); 5.20 (2H, s, NC$\underline{H}_2$Ph); 3.08 (3H, s, NCH_3); 2.5—1.0 (11H, m, cyclo-C_6H_{11})	66.18 (66.11	7.64 7.61	9.65 9.69)
11d	3390, 3190, 1685, 1595, 1510	12.05 (1H, bs, NH); 9.8 (1H, bs, NH); 7.75—7.05 (5H, m, ArH); 2.5—0.75 (11H, m, n-C_5H_{11})			
11e	3370, 3180, 1680, 1595, 1500	12.3 (1H, bs, NH); 9.0 (1H, bs, NH); 7.8—7.1 (10H, m, ArH); 3.70 (2H, s, COC$\underline{H}_2$Ph)			
11f	3380, 3160, 1680, 1590, 1510	12.4 (1H, bs, NH); 8.9 (1H, bs, NH); 7.9—6.9 (5H, m, ArH); 2.5—0.8 (11H, m, cyclo-C_6H_{11})	64.10 (64.13	6.92 6.95	10.68 10.58)
11g	3390, 3200, 1665, 1595, 1510	12.6 (1H, bs, NH); 9.15 (1H, bs, NH); 8.1—7.1 (10H, m, ArH)			
11h	3340, 1710, 1515, 1430, 1385	8.25 (1H, bs, NH); 7.5—6.8 (10H, m, ArH); 3.60 (3H, s, NCH_3); 3.54 (2H, s, COC$\underline{H}_2$Ph)	67.59 (67.59	5.67 5.70	9.85 10.02)
11i	3330, 1710, 1490, 1430, 1400	7.85 (1H, bs, NH); 7.5—6.7 (10H, m, ArH); 4.17 (2H, q, NC$\underline{H}_2CH_3$); 3.54 (2H, s, COC$\underline{H}_2$Ph); 1.20 (3H, t, $NCH_2C\underline{H}_3$)	68.44 (68.46	6.08 6.08	9.39 9.45)
11j	3350, 1705, 1495, 1450, 1400	7.9 (1H, bs, NH); 7.4—6.6 (10H, m, ArH); 5.7—5.1 [1H, m, NC$\underline{H}$(CH_3)C_2H_5]; 3.54 (2H, s, COC$\underline{H}_2$Ph); 1.9—0.7 [8H, m, NCH ($C\underline{H}_3$)$C_2\underline{H}_5$]	69.92 (69.94	6.79 6.78	8.58 8.52)

removal of $Ph_3P{=}O$ and HN=C=S *via* a six-membered cyclic transition state to give an amide (**10**) (route a) and by removal of $Ph_3P{=}O$ *via* a four-membered cyclic transition state to give acylthiourea (**11**) (route b) as shown in Chart 2. As the bulkiness of the substituents in **1** and **9** increases, the formation of amide (**10**) decreases while that of acylthiourea (**11**) increases. This may be rationalized as follows: when the substituents of the amine (**1**) and/or carboxylic acid (**9**) are bulky, steric interference of the RR'N(C=S) and R″ groups in route

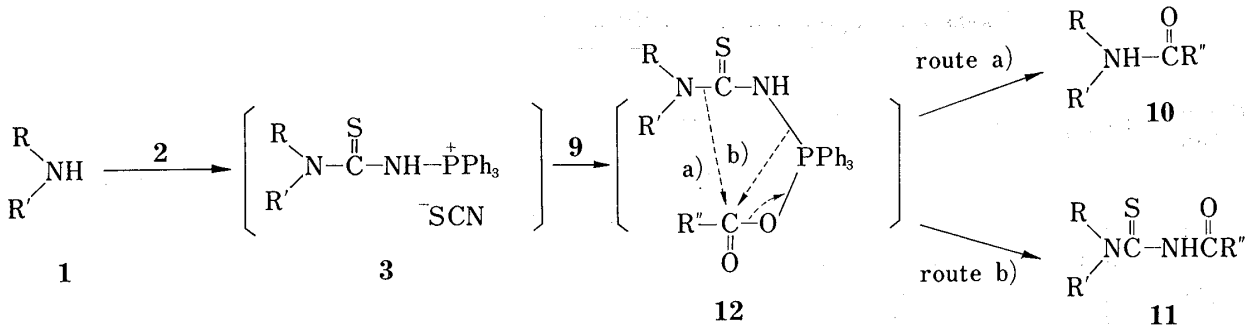

Chart 2

b may be less than that of the RR'N and R″ groups in route a, since in route b the substituents can take a *trans* orientation.

Experimental

All melting and boiling points are uncorrected. The IR spectra were recorded on a Hitachi-G2 spectrometer, and NMR spectra on a Hitachi R-20A spectrometer (with tetramethylsilane as an internal standard). Mass spectra were obtained with a Hitachi RMU-6M instrument with a direct inlet system operating at 70 eV. Column chromatography was carried out on Merck Silica-gel 60.

General Procedures for 1,1-Disubstituted Thioureas (4a—g)——A solution of amine (**1**) (6 mmol) in dry acetonitrile (15 ml) was added to freshly prepared TPPT (**2**) (*ca.* 9 mmol) in dry CH_2Cl_2 (30 ml) at −40° under argon. The mixture was stirred for 2 hr under the same conditions, allowed to warm to room temperature, stirred for 5—24 hr and quenched with 5% aqueous CH_3CN (60 ml). The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica-gel using AcOEt–acetone (2: 1) as a solvent to give the corresponding 1,1-disubstituted thiourea (**4**). Compounds (**4a—f**) were identical with authentic specimens as determined by comparison of their melting points and spectral data. The results are listed in Table I. N-Cyclohexyl-N-methylthiourea (**4g**) gave satisfactory analytical and spectral data: *Anal.* Calcd. for C, 55.79; H, 9.36; N, 16.27. Found: C, 55.57; H, 9.34; N, 15.99.

N-Benzyl-N-methylthiocarbamoyltriphenylphosphinimine (8)——A solution of N-methylbenzylamine (**1a**) (726 mg, 6 mmol) in dry CH_3CN (15 ml) was added to freshly prepared TPPT (**2**) (*ca.* 3 mmol) in dry CH_2Cl_2 (15 ml) at −40° under argon. The mixture was stirred for 1 hr under the same conditions, allowed to warm to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel using C_6H_6–ether (2: 1) as a solvent to give **8** (832 mg, 63%). Recrystallization from C_6H_6–ligroin gave colorless crystals, mp 154—155°. *Anal.* Calcd. for C, 73.74; H, 5.68; N, 6.36. Found: C, 73.74; H, 5.74; N, 6.12. IR ν_{max}^{tablet} cm^{-1}: 1485, 1445, 1430, 1380, 1350, 1275 and 1105; NMR ($CDCl_3$) δ: 8.0—7.0 (20H, m, ArH), 5.3—5.1 (2H, bs, $PhCH_2N$) and 3.35 (3H, bs, NCH_3); MS *m/e* 440 (M^+).

Conversion of 8 to N-Benzyl-N-methylthiourea (4a) by Treatment with Thiocyanic Acid——An aqueous solution of thiocyanic acid (*ca.* 0.3 mmol, 1 ml) was added to a solution of the phosphinimine (**8**) (44 mg, 0.1 mmol) in CH_2Cl_2–CH_3CN (1: 1, 5 ml) at room temperature and the mixture was allowed to stand at room temperature overnight. Concentration of the mixture under reduced pressure gave a residue, which was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel using AcOEt–acetone (2: 1) as a solvent to give the thiourea (**4a**) (10 mg, 56%), which was identical with an authentic specimen in all respects.

General Procedures for Conversion of the Phosphonium Salt (3) into an Amide (10) and/or Acylthiourea (11) by Treatment with a Carboxylic Acid (9)——A solution of **1** (5 mmol) in dry CH_2Cl_2 (15 ml) was added to freshly prepared TPPT (**2**) (*ca.* 6 mmol) in dry CH_2Cl_2 (20 ml) at −40° under argon. After disappearance of the starting amine (**1**) (monitored by TLC), a solution of carboxylic acid (**9**) (5 mmol) in dry CH_2Cl_2 (15 ml) was added to the mixture and it was allowed to stand at room temperature overnight. After removal of the solvent under reduced pressure, the residue was subjected to column chromatography on silica-gel using AcOEt–*n*·hexane (1: 2) as a solvent to give the amide (**10**) and/or acylthiourea (**11**). The results are listed in Table II and Table III.

Conversion of 8 into the Amide (10a) and Acylthiourea (11a) by Treatment with Phenylacetic Acid (9a)——A mixture of **8** (440 mg, 1 mmol) and **9a** (136 mg, 1 mmol) in dry CH_2Cl_2 (8 ml) was allowed to stand at room temperature overnight, then concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel using AcOEt–*n*·hexane (1: 2) to give **10a** (88 mg, 30%) and **11a** (55 mg, 23%) together with **4a** (34 mg, 18%). These compounds were identical with authentic specimens in all respects.