Reaction of Grignard Reagents with the Combined Reagent Triphenylphosphine Thiocyanate; A Versatile Route to *N*-Unsubstituted Thioamides

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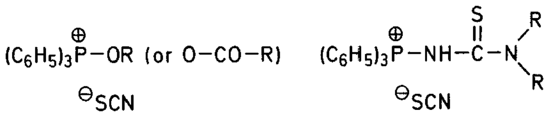
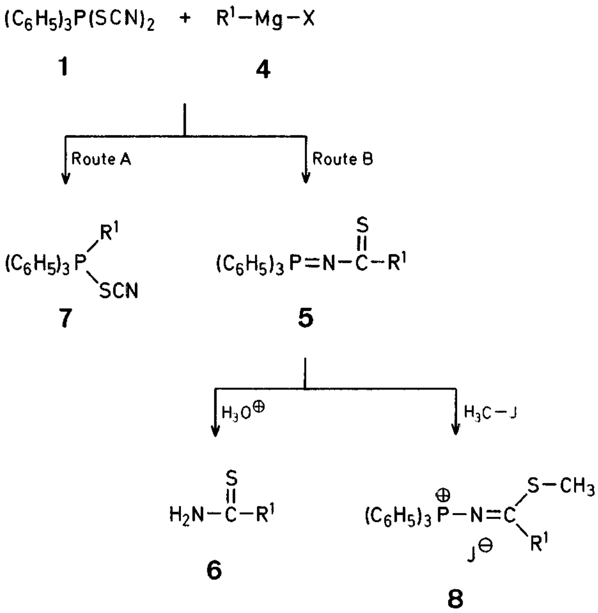
Recently, reactions of the combined reagent triphenylphosphine thiocyanate $(C_6H_5)_3P(SCN)_2$ (**1**) with some nucleophiles have been studied extensively[1-4] and were classified by the following two features: (a) as observed in the reaction with alcohols[1], carboxylic acids[2], and epoxides[3], nucleophilic attack on the phosphorus atom of **1** followed by substitution of the SCN anion on the adjacent carbon to oxygen atom of the intermediates **2** with elimination of triphenylphosphine oxide, giving the thio- and/or isothiocyanates (Route A) and (b) as observed in the reaction with amines[4], nucleophilic addition on the —N=C=S carbon of **1** and subsequent hydrolysis of the N—P$^{\oplus}$ bond of the intermediates **3**, giving thioureas (Route B). These interesting reactivities of **1** toward nucleophiles led us to investigate the reactions with organometallic compounds and we have now found that the reaction of **1** with Grignard reagents **4** proceeds mainly by Route B to give the phosphinimine intermediates **5** which, on acid hydrolysis *in situ*, undergo spontaneous elimination of triphenylphosphine oxide to give the corresponding *N*-unsubstituted thioamides **6** in fair yields.



2 **3**



In a typical reaction, benzylmagnesium chloride (**4a**; 1 equiv) was allowed to react with **1** (1.3 equiv) under argon at −40° for 1 h and the reaction mixture was treated with aqueous hydrochloric acid at room temperature to give benzylthioamide **6a**. Without work-up with aqueous hy-

Table. Thioamides **6** Prepared

Product[a]	Grignard reagent **4**	Yield [%] of **6**	m.p. (solvent) or b.p./torr[b]	Lit. m.p. or b.p./torr	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
6a	$C_6H_5CH_2$—MgCl	58	94–96° (benzene/*n*-hexane)	96–97°[5]	3530; 3360; 1600; 1400	7.5–6.4 (b, 2H, NH_2); 7.29 (s, $5H_{arom}$); 4.06 (s, 2H, CH_2—C_6H_5)
6b	C_2H_5—MgBr	42	92–96°/0.1	80°/0.05[7] m.p. 42–43°[6]	3480; 3360; 1605; 1405	8.9–6.5 (b, 2H, NH_2); 2.69 (q, 2H, CS—CH_2); 2.30 (t, 3H, CH_3)
6c	*n*-C_3H_7—MgCl	53	80–84°/0.1	88.5°/0.11[7]	3480; 3360; 1605; 1400	8.8–6.8 (b, 2H, NH_2); 2.64 (t, 2H, CS—CH_2); 1.77 (m, 2H, CH_2CH_3); 0.97 (t, 3H, CH_2CH_3)
6d	*i*-C_3H_7—MgBr	61	90–94°/0.1	85.5°/0.1[7]	3480; 3360; 1600; 1410	8.9–7.2 (b, 2H, NH_2); 2.92 [m, 1H, CS—$CH(CH_3)_2$]; 1.25 [d, 6H, $CH(CH_3)_2$]
6e	*n*-C_4H_9—MgBr	66	94–98°/0.1	94°/0.05[7]	3480; 3360; 1605; 1400	8.6–7.1 (b, 2H, NH_2); 2.65 (t, 2H, CS—CH_2); 2.1–0.6 (m, 7H, *n*-C_3H_7)
6f	*i*-C_4H_9—MgCl	89	55–56° (benzene/PE)	47°[7]	3480; 3360; 1605; 1400	8.6–6.8 (b, 2H, NH_2); 2.50 (d, 2H, CS—CH_2); 2.65–1.85 [m, 1H, $CH(CH_3)_2$]; 0.96 [d, 6H, $CH(CH_3)_2$]
6g	*n*-C_6H_{13}—MgCl	60	53.5–54.5° (PE)	—[8]	3480; 3360; 1605; 1400	8.5–6.5 (b, 2H, NH_2); 2.65 (t, 2H, CS—CH_2); 2.1–0.6 (m, 11H, *n*-C_5H_{11})
6h	*n*-C_8H_{17}—MgCl	62	72–73.5° (*n*-hexane)	—[c]	3480; 3360; 1605; 1400	8.2–6.5 (b, 2H, NH_2); 2.65 (t, 2H, CS—CH_2); 2.1–0.6 (m, 15H, *n*-C_7H_{15})

[a] Purity of products ≥95% as determined by I.R. and ^{1}H-N.M.R. analysis; microanalyses were in satisfactory agreement with the calculated values (C ±0.10, H ±0.09, N ±0.21).

[b] Bath temperature.

[c] $C_9H_{19}NS$ (173.3) calc. C 62.39 H 11.05 N 8.09; found 62.29 11.14 7.88

drochloric acid, the phosphinimine intermediate **5a** and the phosphonium salt **7** were isolated in 31% and 8% yields, respectively. The structure of compound **5a** was deduced from spectral data [I.R. ($CHCl_3$): ν=1440, 1405, 1115 cm^{-1}; ^{1}H-N.M.R. ($CDCl_3$): δ=8.0–7.0 (m, $20H_{arom}$), 4.22 ppm (d, 2H, P=N—CS—CH_2, J=2.5 Hz); M.S.: m/e=411 (M^+)] and established by its quantitative conversion into benzylthioamide **6a** on treatment with hydrochloric acid and into the *S*-methylated phosphonium salt **8** on treatment with methyl iodide. Similarly, various Grignard reagents **4b–h** were allowed to react with **1**, followed by treatment with aqueous hydrochloric acid to give the thioamides **6b–h.** The results are given in the Table.

The present method, to our knowledge, is superior to those reported[10–15] previously for the preparation of thioamides **6** because of the ease of performance and work-up, the mild reaction conditions, and the fair yields of the products. Moreover, the isolation of compound **7** (an analog of **2**) is significant since the phosphonium salts **2** have been considered as the initial products for the thio- and/or isothiocyanation in Route A but have not been isolated yet.

Thioamides 6; General Procedure:

The triphenylphosphine thiocyanate (**1**) in benzene/ether/tetrahydrofuran is prepared by the modification of the previous method[1]: Thiocyanogen, generated from lead thiocyanate (excess) and bromine (4 mmol) in benzene (5 ml), is diluted with ether/tetrahydrofuran (3:1, 20 ml). To this solution, an equimolar amount of triphenylphosphine (4 mmol) in ether/tetrahydrofuran (1:1, 20 ml) is added with stirring at −40°. Stirring is continued for 1 h at the same temperature to give the desired reagent. To a stirred solution of the freshly prepared reagent (~4 mmol) in benzene/ether/tetrahydrofuran (1:5:3, 45 ml), a solution of Grignard reagent **4** (3 mmol) in dry ether (3–4 ml) is added at −40° under argon. Stirring is continued for 1 h under the same conditions. The mixture is allowed to warm to room temperature, quenched with 10% hydrochloric acid (5 ml), and kept at room temperature overnight. The organic layer is evaporated under reduced pressure. The residual product is purified by column chromatography on silica gel using chloroform or dichloromethane as eluent to give the thioamide **6**. Pure samples are obtained by recrystallization or distillation under the conditions listed in the Table.

***N*-(1-Phenylthioacetyl)-phosphinimine (5a) and Phosphonium Salt (7):**

The 0.5 molar Grignard reagent solution **4a** (5 ml, 2.5 mmol) is allowed to react with triphenylphosphine thiocyanate (~3 mmol) under the conditions as above. Instead of work-up with 10% hydrochloric acid, the mixture is quenched with water (5 ml). The organic layer is dried with magnesium sulfate. Addition of dry ether (40 ml) gives a precipitate which is filtered and recrystallized from ethanol/ethyl acetate to give **7**; yield: 100 mg (8%); m.p. 193–195° (Lit.[9], 189°).

I.R. ($CHCl_3$): ν=2130, 1435, 1110 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ=7.9–6.8 (m, 20H); 4.98 ppm (d, J=14.5 Hz, 2H).

The filtrate is evaporated under reduced pressure. The residual product is purified by column chromatography on silica gel using benzene as an eluent to give *N*-(1-phenylthioacetyl)-phosphinimine **5a**; yield: 322 mg (31%); m.p. 111–113°.

Hydrolysis of 5a to 6a:

To a solution of the phosphinimine **5a** (100 mg, 0.24 mmol) in ether (4 ml) and dioxan (4 ml), 10% hydrochloric acid (2 ml) is added. The mixture is stirred at room temperature for 3 h and then diluted with ether (20 ml). The organic layer is dried with magnesium sulfate and evaporated under reduced pressure. The residual product is purified by column chromatography on silica gel using chloroform as an eluent to give **6a**; yield: 34 mg (92%); m.p. 94–96°.

Methylation of 5a to 8:

To a solution of the phosphinimine **5a** (202 mg, 0.49 mmol) in dry dichloromethane (3 ml), methyl iodide (0.5 ml) is added. The mixture is allowed to stand at room temperature and evaporated under reduced pressure to give a crystalline mass. Recrystallization from methanol gives the *S*-methylated phosphonium salt **8**; yield: 269 mg (99%); m.p. 204–207° (dec.).

$C_{27}H_{25}JNPS$ (553.5)	calc.	C 58.60	H 4.55	N 2.53
	found	58.42	4.39	2.69

I.R. ($CHCl_3$): ν=1580; 1560; 1440; 1110 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta=7.9-6.9$ (m, 20H); 4.02 (s, 2H); 2.82 ppm (s, 3H).

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[1] Y. Tamura, T. Kawasaki, M. Adachi, M. Tanio, Y. Kita, *Tetrahedron Lett.* **1977**, 4417.
J. Burski, J. Kieszkowski, J. Michalski, M. Pakulski, A. Skowrońska, *J. Chem. Soc. Chem. Commun.* **1978**, 940.

[2] Y. Tamura, T. Kawasaki, M. Tanio, Y. Kita, *Chem. Ind. (London)* **1978**, 806.

[3] Y. Tamura, T. Kawasaki, N. Gohda, Y. Kita, *Tetrahedron Lett.* **1979**, 1129.

[4] Y. Tamura, M. Adachi, T. Kawasaki, Y. Kita, *Tetrahedron Lett.* **1978**, 1753.
Y. Tamura, T. Kawasaki, M. Tanio, Y. Kita, *Synthesis* **1979**, 120.
Y. Tamura, T. Kawasaki, M. Adachi, Y. Kita, *Chem. Pharm. Bull.* **27**, 1636 (1979).

[5] L. Cassar, S. Panossian, C. Giordano, *Synthesis* **1978**, 917.

[6] A. W. Ralston, R. J. VanderWal, M. R. McCorkle, *J. Org. Chem.* **4**, 68 (1939).

[7] P. Reynaud, R. C. Moreau, P. Fodor, *C. R. Acad. Sci. Paris Ser. C* **264**, 1414 (1967); *C. A.* **68**, 59065 (1968).

[8] C. Francois, L. M. Odile, *U. S. Patent* 3882110 (1975); *C. A.* **83**, 58803 (1975).

[9] A. Michaelis, H. V. Soden, *Justus Liebigs Ann. Chem.* **229**, 295 (1885).

[10] For review; R. N. Hurd, G. Delamater, *Chem. Rev.* **61**, 45 (1961).
W. Walter, K.-D. Bode, *Angew. Chem.* **78**, 517 (1966); *Angew. Chem. Int. Ed. Engl.* **5**, 447 (1966).
To date, *N*-unsubstituted thioamides have been prepared by reaction of amides with phosphorus pentasulfide[11], by reaction of nitriles with hydrogen sulfide[12], and by reaction of aromatic hydrocarbons or carbanions with isothiocyanates substituted with hydrolyzable groups such as *N*-ethoxycarbonyl[13], *N*-benzoyl[14], or *N*-trimethylsilyl group[15] followed by liberation of the substituent.

[11] A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **11**, 338 (1878).

[12] M. A. McCall, *J. Org. Chem.* **27**, 2433 (1962).

[13] E. P. Papadopoulos, *J. Org. Chem.* **41**, 962 (1976).

[14] W. Walter, J. Krohn, *Justus Liebigs Ann. Chem.* **1973**, 476.

[15] A. C. W. Curran, R. G. Shepherd, *J. Chem. Soc. Perkin Trans. 1* **1976**, 983.

0039-7881/79/1132-0889 $ 03.00