The Improved Phosphoramidate Route to Isothiocyanates

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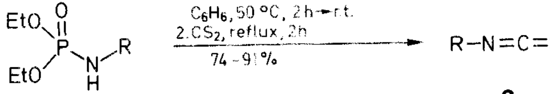
Moderate yields of isothiocyanates prepared by the Wadsworth-Emmons approach can be essentially improved when the reaction is carried out in the presence of catalytic amounts of tetrabutylammonium bromide.

Although a variety of synthetic procedures leading to isothiocyanates have been described[1] simple and general access to this class of compounds starting from easily available substrates is still lacking. The recommended[2] Wadsworth-Emmons phosphoramidate approach[3] suffers from variable, sometimes low yields, and evident difficulties in reproducing the reported experimental results.

Recently a general and straightforward protocol for transforming alkyl bromides into diethyl alkylphosphoramidates **1** via the intermediately formed alkyl azides and the corresponding triethyl (alkylimido)phosphate became available.[4] Ready access to this class of compounds opened new synthetic perspectives before the phosphoramidate approach to various unsaturated organic nitrogen derivatives. It appeared reasonable to reinvestigate *inter alia* the synthesis of isothiocyanates based on phosphoramidate anions attempting to optimize the reaction conditions. Previous studies from this laboratory established that the nucleophilic reactivity of sodium alkyl(diethoxyphosphoryl)amide can be drastically increased by adding catalytic amounts of tetrabutylammonium bromide to the reaction mixture.[5] This spectacular catalytic action is not quite clear but it may possibly involve the formation of loose, highly reactive ion-pairs in the reaction medium under the influence of the catalyst. Application of this specific catalysis for the reaction between



1 **2**

1, 2	R	1, 2	R
a	Ph	**d**	c-C_6H_{11}
b	n-Bu	**e**	c-C_5H_9
c	$PhCH_2$	**f**	i-Bu

sodium alkyl(diethoxyphosphoryl)amide and carbon disulfide should in our opinion markedly increase the yield of isothiocyanates. Corroboration of this conjecture is demonstrated in this paper.

It was found that diethyl alkylphosphoramidates **1** react easily with carbon disulfide in boiling benzene after their deprotonation under anhydrous conditions by means of sodium hydride. Alkyl (aryl) isothiocyanates **2** formed can be readily isolated by evaporation of the solvent and extraction of the residue with hexane followed by distillation *in vacuo*. When the reaction is carried out in the presence of 5 mol% of tetrabutylammonium bromide practically pure **2** (95–98% purity as determined by GLC) are produced in high yields (74–91%, see Table). Inferior results (30–50% yield) of contaminated products **2** are obtained in the absence of tetrabutylammonium bromide. Phenyl isothiocyanate (**2a**) can also be obtained, although in lower yield (48%) by the phase-transfer catalyzed (PTC) variant of the Wadsworth–Emmons reaction using solid, powdered sodium hydroxide/potassium carbonate as base. However, attempted application of this procedure for the synthesis of alkyl/aryl isothiocyanates **2b–f** failed, possibly due to insufficient acidity of the starting phosphoramidates **1b–f**. The reported modified phosphoramidate route to isothiocyanates can successfully compete with other synthetic procedures disclosed in the literature.

Table. Alkyl/Aryl Isothiocyanates **2**

Product	Yield[a,b] (%)	bp (°C)/Torr	n_D^{20}	Literature Data	
				bp (°C)/Torr	n_D^{20}
2a	83 (30)	96–99/15	1.6478	96–98/15[6]	1.6508,[7] $n_D^{23.4}$ = 1.6492[8]
2b	91 (75)	45–47/10	1.4980	47–48/10[6]	1.5010[7]
2c	76	125–130/15	1.5975	126–128/14[9]	1.6039[10]
2d	84 (71)	100–105/10	1.5320	109/10[6]	1.5381[7]
2e	91[c]	95–100/25	1.5231	80/10[11]	
2f	74	47–52/20	1.4980	85/47[12]	n_D^{14} = 1.5005[8]

[a] Yield of distilled product. Yields of isothiocyanates reported by Wadsworth and Emmons[3] are shown in parenthesis.

[b] All compounds exhibited strong absorption bands at 2150 cm^{-1} in their IR spectra.

[c] Product contaminated with ca. 10% of an unknown impurity (GLC).

Alkyl/Aryl Isothiocyanates 2; General Procedure:

A solution of diethyl alkyl/arylphosphoramidate (**1**; 0.04 mol) in benzene (50 mL) is added dropwise with stirring to a suspension of NaH (1.2 g, 0.05 mol; freshly separated from paraffin oil by washing with hexene) and n-Bu_4NBr^- (0.64 g, 5 mol%) in benzene (150 mL) during 30 min at 50 °C. After evolution of H_2 has ceased (ca. 2 h) the mixture is cooled to r.t., and CS_2 (6.1 g, 0.08 mol) is added in one portion. The mixture is then refluxed for 2 h and left overnight at 20–25 °C. The resultant solution is filtered and evaporated under reduced pressure. The oily residue is extracted with hexane (2 × 50 mL), the extract is filtered again, washed with H_2O (2 × 50 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Crude isothiocyanates **2** are purified by distillation *in vacuo*. Yields and physical constants of pure **2** are compiled in the Table.

Preparation of Phenyl Isothiocyanate (2a) Under PTC Conditions:

A mixture of diethyl phenylphosphoramidate (**1a**; 4.6 g, 0.02 mol), n-Bu_4NBr^- (0.64 g, 10 mol/, powdered NaOH (3.2 g, 0.08 mol), K_2CO_3 (8.3 g, 0.06 mol), CS_2 (3.1 g, 0.04 mol), and benzene (100 mL) is refluxed for 2 h with efficient stirring. The resultant mixture is cooled to r.t. and treated with H_2O (150 mL). The organic layer is washed with H_2O (2 × 50 mL), dried ($MgSO_4$), evaporated, and distilled *in vacuo*; yield: 1.3 g (48%); bp 96–98 °C/15 Torr.

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