A New Synthesis of Aliphatic Isothiocyanates from Primary Amines, Convenient for *In Situ* Use

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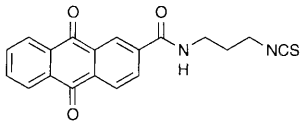
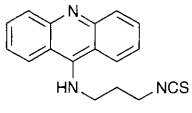
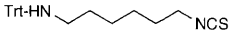
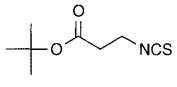
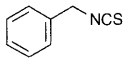
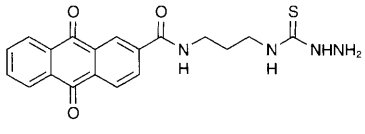
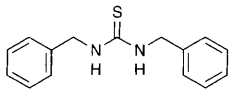
Primary aliphatic amines react with carbon disulfide in the presence of BOP (benzotriazole-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate **1**, giving the corresponding isothiocyanates in good to high yields and high purity; a number of isothiocyanates are synthesized and isolated or generated *in situ* and treated with a nucleophile.

Methods to quickly synthesize aliphatic isothiocyanates from the corresponding amines, under mild conditions are of great value. Many reagents have been used for this purpose, starting with thiophosgene[1,2] and derivatives of thiophosgene such as thiocarbonyldi-(1,2,4-triazole)[3] and 1-dipyridyl thionocarbonate.[4] These are very powerful reagents for introduction of a thiocarbonyl group. On the other hand the specificity of these reagents limits their scope. Alternative reagents, such as dicyclohexylcarbodiimide[5] have also been applied with some success, although reaction times as long as twelve hours are required. In our attempts to synthesize *N*-(3-isothiocyanatopropyl)-2-anthraquinone carboxamide (compound **2**, Table 1) several of the above mentioned methods were tried without success. By treating the corresponding primary amine with carbon disulfide and BOP in DMF, a quantitative yield of the isothiocyanate was obtained. BOP is a widely used coupling reagent in peptide synthesis,[6,7] but has also been used in convenient syntheses of phenyl esters[8] and thioamides.[9,10]

The synthesis of isothiocyanates by the use of BOP and carbon disulfide proceeds smoothly at room temperature in apolar solvents such as dichloromethane, or in dipolar aprotic solvents such as DMF or Me_2SO. Different work-up procedures can be used depending on the solvent and nature of the product. The method is compatible with a variety of protecting groups and even very acid labile protecting groups, such as the triphenylmethyl group or the base labile methyl ester group, are not affected during the reaction.[11] The method could therefore potentially be used to synthesize isothiocyanates of complicated molecules containing multiple protected functional groups. The isothiocyanate can either be isolated, or generated *in situ*, followed by direct reaction with a nucleophile.

In the general procedure (Scheme 1), carbon disulfide (10 mmol) was dissolved in of DMF (5 ml). Then the aliphatic amine (1 mmol) followed by BOP (1 mmol) was added and the reaction mixture stirred for 30 min at room temperature. If the amine was used as the hydrochloride, 3 equiv. of triethylamine were added to initiate the reaction. Excess carbon disulfide was removed *in vacuo* and 5 ml of water added while cooling on an ice-bath. If the isothiocyanate precipitated as a solid (compound **2**, **3** and **4**) it was collected by filtration and washed several times with water. If the isothiocyanate came out as an oil (compound **5** and **6**), the water/DMF fraction was extracted with

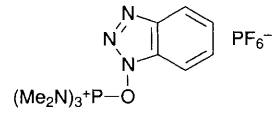
Table 1 Yields and analytical data for the synthesized compounds. ^1H NMR were run at 400 MHz Varian Unity apparatus with $(CD_3)_2SO$ as solvent (except for compound **3** for which $CDCl_3$ was used as solvent). All mps were measured on a Büchi apparatus, and are uncorrected. MS were in accordance with the expected values

	Compound	Yield (%)	mp/bp/°C (*p*/mmHg)	^1H NMR (δ)
2		97	mp: 169–172	9.10 (t, 1 H), 8.75 (s, 1 H) 8.30 (m, 4 H), 7.90 (m, 2 H), 3.80 (t, 2 H), 3.40 (q, 2 H), 1.90 (qn, 2 H)
3[a]		74	mp: 228–230 (decomp.)	8.20 (d, 2 H), 8.00 (d, 2 H), 7.90 (t, 2 H), 7.60 (t, 2 H), 4.20 (br, t, 1 H), 3.70 (t, 2 H), 3.50 (t, 2 H), 2.10 (qn, 2 H)
4		69	mp: 128–131	7.50–7.20 (m, 15 H), 3.50 (t, 2 H), 2.90 (t, 2 H), 2.10 (m, 4 H), 1.60 (qn, 2 H), 1.30 (qn, 2 H), 1.20 (qn, 2 H)
5[b]		78	bp: 93–95 (2)	3.80 (t, 2 H), 2.60 (t, 2 H), 1.45 (s, 9 H)
6		63	bp: 80–82 (2)	7.30 (m, 5 H), 4.90 (s, 2 H)
7		74	mp: 202–205 (decomp.)	9.00 (t, 1 H), 8.60 (s, 1 H), 8.30 (m, 4 H), 8.05 (br, s, 1 H), 7.90 (m, 2 H), 4.50 (s, 2 H), 3.50 (dt, 2 H), 3.40 (t, 2 H) 1.80 (qn, 2 H)
8		64	mp: 146–148	7.95 (br, s, 4 H), 7.20 (m, 10 H), 4.65 (s, 4 H)

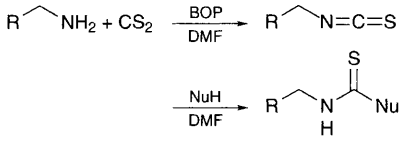
[a] Me_2SO was used as solvent. [b] Backwashing of the ether fraction was omitted, the ether was evaporated *in vacuo* and the product purified by vacuum distillation.

diethyl ether (5 × 10 ml). The combined ether fractions were backwashed once with water (50 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the isothiocyanate purified by distillation at reduced pressure. The isothiocyanates were isolated in good to high yields and were of high purity (Table 1).

The thiosemicarbazide (compound **7**) was synthesized by adding the reaction mixture—containing the isothiocyanate—to a stirred solution of excess hydrazine hydrate (12 equiv.) in DMF at 4 °C. The reaction mixture was stirred overnight at room temperature and the product precipitated by the addition of water. Dibenzyl thiourea (compound **8**) was synthesized by adding excess benzyl amine (10 equiv.) to the reaction mixture. Water was then added and the product precipitated as an oil which gradually solidified. The crude product was recrystallized from ethanol/water (6 : 4). Both compounds are isolated in good yields.



1



Scheme 1

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