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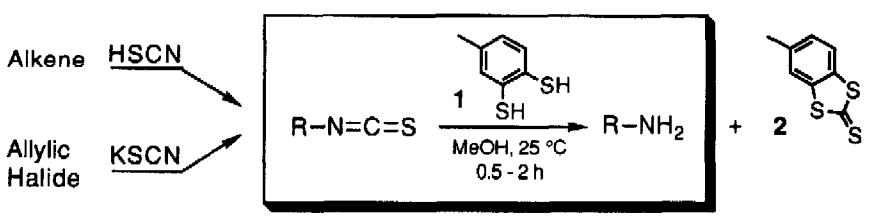
ALKYL AND ARYL ISOTHIOCYANATES AS MASKED PRIMARY AMINES

Cheon-Gyu Cho and Gary H. Posner,*
Department of Chemistry, School of Art and Sciences,
The Johns Hopkins University, Baltimore, MD 21218, USA

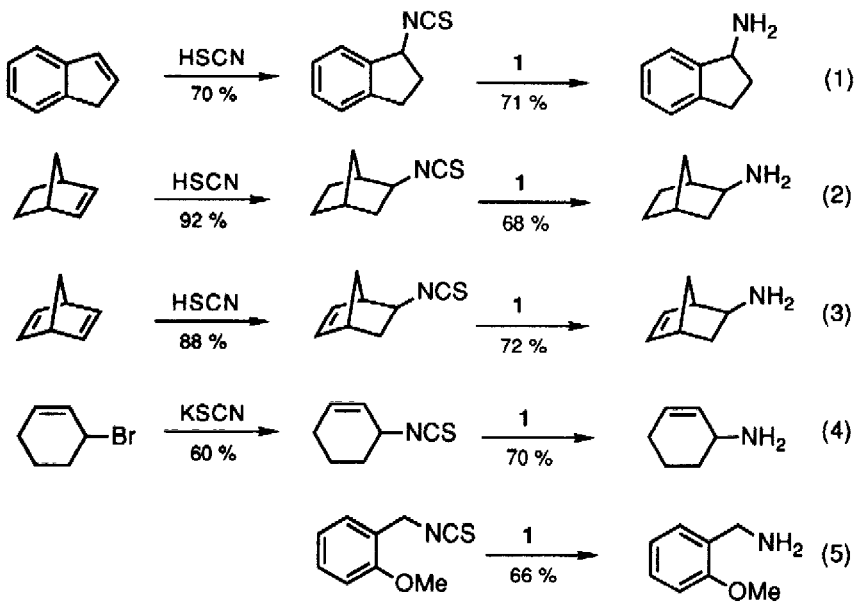
Abstract: Primary and secondary (but not tertiary) alkyl as well as aryl isothiocyanates react rapidly with 4-methyl-1,2-benzenedithiol (**1**) in methanol at room temperature, releasing the corresponding amines in good yields. This mild and simple procedure for unmasking amines proceeds chemospecifically with isothiocyanates even in the presence of such normally electrophilic and reactive functionalities as carboxylate ester and N-alkylphthalimide.

In connection with a research program involving extraction, isolation, and identification of plant constituents that are chemoprotective against cancer,[1] a new chemical reaction of isothiocyanates with aliphatic and aromatic 1,2-dithiols has been discovered leading to cyclic trithiocarbonates, probably *via* thiocarbamate intermediates.[2] Condensation of primary and secondary alkyl as well as aryl isothiocyanates with 1,2-benzenedithiol and with 4-methyl-1,2-benzenedithiol (**1**), proceeding rapidly and completely in methanol at room temperature, produced yellow trithiocarbonates (e.g. **2**) with UV absorptions at 365-367 nm and with high extinction coefficients (a_m 23,000 M^{-1} cm^{-1}, **Scheme I**). These cyclocondensations are now the basis of a reliable and sensitive new spectroscopic method for convenient UV monitoring of the progress of these cyclocondensations as well as for quantitative UV analysis of organic isothiocyanates,[2] one of which (sulforaphane) was isolated from broccoli and was found to be a major inducer of anticarcinogenic protective enzymes.[1] Herein we report on the complementary use of isothiocyanates as synthetic equivalents (i.e. precursors) of primary amines (**Scheme I**). Also, the isothiocyanate protecting group is shown to be susceptible to chemospecific unmasking in the presence of other normally reactive functionalities such as carboxylate ester or phthalimide, a well established amine protecting group.

Scheme I

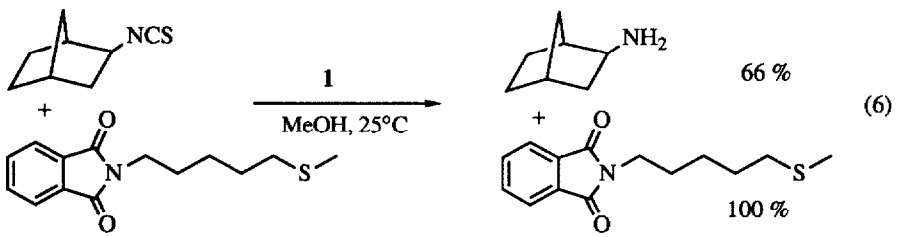


Secondary alkyl isothiocyanates were prepared, according to literature precedents,[3,4] by addition of HSCN to polarized (eq.1) and to ring-strained carbon-carbon double bonds (eqs 2, 3). Unactivated alkenes[5] (e.g. cyclohexene) were not susceptible to HSCN addition. Reaction of these isothiocyanates with 1.2 equivalents of odorless dithiol **1** in methanol at 25°C gave within 0.5-2 hours the corresponding amines conveniently on gram scale in good yields (eq. 1-3). Although tertiary alkyl isothiocyanates could also be prepared *via* HSCN addition to several trisubstituted alkenes, the amine unmasking step using dithiol **1** could not be realized even under forcing conditions. Also, KSCN displacement of an allylic bromide followed literature analogy[5] to give, after thermal rearrangement of the initial mixture of thiocyanate and isothiocyanate substitution products, an allylic isothiocyanate that underwent smooth unmasking with dithiol **1** to liberate an allylic amine (eq. 4). Primary alkyl isothiocyanates also successfully underwent this unmasking procedure, although the reaction of the somewhat sterically inaccessible primary isothiocyanate in eq. 5 required a catalytic amount of aqueous sodium bicarbonate in order for complete unmasking to occur within 2 hours. 1,3-Benzenedithiol, a non-*vicinal* dithiol, was not effective in liberating amines from isothiocyanates, and aliphatic 1,2-dithiols (e.g. 1,2-ethanedithiol or 2,3-dimercaptopropanol) were much less effective than aromatic 1,2-dithiols, even though these aliphatic 1,2-dithiols did react with isothiocyanates forming spectroscopically detectable thiocarbamates.[2] The success of aromatic dithiols such as **1** in liberating amines from isothiocyanates is undoubtedly due in large part to a favorable entropy factor in the final cyclization step; it was for this reason that we originally examined aromatic 1,2-dithiols. The overall yields in eqs. 1-4 (42-60 %) matched and often exceeded those reported in the literature for other reaction sequences generally used for converting alkenes or allylic halides into amines.[3,5,7] The product amines in eqs. 1-5 were fully characterized spectroscopically and physically.[8]

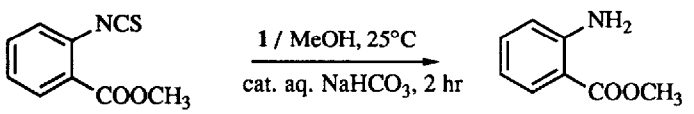


Although isothiocyanates have previously been converted into amines, reaction conditions are usually harsh, normally involving strong acids or strong bases.[3a,9] **The mild, non-aqueous, and neutral conditions characteristic of these conversions of isothiocyanates into amines recommend this aromatic dithiol procedure as a new and useful synthetic transformation.**

Finally, the inertness of many normally reactive functional groups (e.g. thiocyanate, nitrile, carboxylate ester, imide, primary alkyl bromide, ketal) toward aromatic dithiols such as **1** for 2 hours at 25 °C allows highly chemoselective unmasking of isothiocyanates in the presence of such functional groups. For examples, a phthalimide, a typical amine protecting group,[10] was found to be inert to dithiol **1** under conditions in which an isothiocyanate was unmasked (eq. 6); in contrast, both phthalimide and isothiocyanate were consumed by hydrazine, a reagent used normally to unmask phthalimides.[10] Also, a bifunctional carboxylate ester aryl isothiocyanate[11] was chemospecifically unmasked into the corresponding amino ester under sufficiently mild and non-hydrolytic conditions so that the ester survived (eq. 7).



(6)



(7)

In conclusion, 4-methyl-1,2-benzenedithiol (**1**) has been shown to be a particularly effective reagent for mild, rapid, usually neutral and operationally convenient liberation of primary amines from isothiocyanates even in the presence of other normally reactive functional groups. Other applications of this procedure for synthesis of amines are anticipated.[12,13]

Acknowledgment

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8. TYPICAL EXPERIMENT; To a magnetically stirred solution of 2.42 g (13.81 mmol) of 1-isothiocyanatoindane (see eq. 1) in 5 ml of MeOH was added 2.59 g of freshly distilled (100-110 °C at 3 mm Hg) 4-methyl-1,2-bezenedithiol (**1**) in 15 ml of MeOH at room temperature. Similar results have been obtained using undistilled, commercial dithiol **1**. After 35 min, a rapid and dramatic formation of a yellow solid (trithiocarbonate **2**, *vide infra*) was observed, with enough heat evolved to reflux the solution. Smaller scale reations (e.g. 0.5-1 mmol) proceeded at room temperature with much less heat generated. The reaction mixture was stirred for another 5 min until no starting isothiocyanate was detected on tlc, and then filtered with a fritted glass funnel, and the yellow cake was washed thoroughly with cold MeOH. The combined methanol solution was concentrated *in vacuo* and chromatographed (100 % EtOAc → 80/20 EtOAc/MeOH with 1 % v/v of Et_3N) to give 1.30 g (9.80 mmol, 71 %) of 1-aminoindane as a liquid. Spectral data matched those of the commercially available authentic sample. Trithiocarbonate **2** (5-methyl-1,3-benzodithole-2-thione), obtained in quantitative yield, was fully characterized, and its physical and spectral properties matched the literature values (Bajwa, G. H.; Berlin, K. D. *J. Org. Chem.* **1976**, *41*, 145).

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