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A new application for diethyl azodicarboxylate: efficient and regioselective thiocyanation of aromatics amines

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ABSTRACT

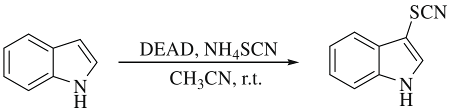
Highly *regioselective thiocyanations* of indoles, anilines and pyrrole are achieved via an efficient and simple protocol using NH_4SCN and diethyl azodicarboxylate (DEAD) as a mild oxidant.

Significant attention is being devoted to organosulfur compounds. Among these compounds, thiocyanates play an important role in organic synthesis[1] and in pharmaceuticals.[2] Thiocyano substituted compounds are useful intermediates in the synthesis of sulfur-containing heterocycles, in which the thiocyanate group can be readily transferred to other sulfur-bearing functionalities such as sulfides,[3] cyanothiolated compounds,[4] or desulfurated to nitriles.[5] Aromatic thiocyanates have become important intermediates for the preparation of heterocycles, especially as precursors for agrochemicals, dyes, and drugs.[6] Due to the versatility of the thiocyanate group in heterocyclic chemistry, various methods have been developed for the thiocyanation of arenes; these include the use of $FeCl_3$,[7] Oxone,[8] I_2/MeOH,[2] ceric ammonium nitrate,[9] *N*-thiocyanatosuccinimide,[10] DDQ[11a] and ultrasound-assisted thiocyanation via DDQ,[11b] montmorillonite K10 clay,[12] electrochemical thiocyanation via SCN^-,[13] and $Mn(OAc)_3$.[14] However, difficulties associated with the use of these reagents include the use of strongly acidic or oxidizing conditions, low overall yields, high temperatures and long reaction times. Diethyl azodicarboxylate (DEAD) is a valuable reagent in organic synthesis especially with reference to the Mitsunobu reaction.[15] Recently, Grée and Cao disclosed an expedient approach to ketones by oxidation of alcohols with DEAD.[16] Thus, in continuation of our work on thiocyanation,[17] we were interested in the application of DEAD as a mild oxidant for aromatic thiocyanation. In the present work, we describe an efficient protocol for the selective thiocyanation of indoles, pyrrole and anilines using NH_4SCN and DEAD.

To identify new conditions for the synthesis of aryl thiocyanates, we began with an investigation of the conversion of indole into its corresponding indole thiocyanate using DEAD and NH_4SCN as a model reaction (Scheme 1).

A solvent screen revealed that acetonitrile was the best for this reaction. The stoichiometry of the reactants was also varied. A ratio of 1:1.8:2.5 (indole:DEAD:NH_4SCN) was found to be the most suitable, and decreasing the amount of DEAD or ammonium thiocyanate increased the reaction time and lowered the yield. The substrate scope of this reaction was then examined using various arenes under the optimized conditions, Table 1.

In general, this reaction provided good-to-excellent yields with all the substrates tested.[18] As shown in Table 1, electron-rich indoles gave the desired products in excellent yields (Table 1, entries 2 and 6). Also, electron- deficient indoles such as 5-bromo- and 5-nitroindole reacted with ammonium thiocyanate and DEAD to afford the corresponding 3-thiocyanatoindole derivatives **1c** and **1d** in good yields, but required longer reaction times (Table 1, entries 3 and 4). This observation can be attributed to the lower electron density of such substrates. The addition was highly regioselective occurring at the 3-position of the indole ring.[8,14] Next, various anilines were converted into the respective 4-thiocyanatoanilines **1g**–**l** in high to excellent overall yields (Table 1, entries 7–12). The reactions were clean and the products were obtained with high *para*-selectivity. However, in the case of a *para*-substituted aniline (Table 1, entry 14), *ortho* thiocyanation occurred in high yield. We also used 3-methoxyaniline as a substrate for the electrophilic thiocyanation reaction, however, no reaction was observed (Table 1, entry 13). Pyrrole was easily transformed into the mono-thiocyanated product (**1n**) within 2.5 h. For construction of a dithiocyanated pyrrole **1n**′ a longer reaction time was required (15 h). Under optimized conditions, when phenol or anisole was used as the substrate, no reaction occurred and the starting materials were recovered after periods of up to two days. In comparison with the reported method using DDQ which requires refluxing conditions[11a] for some substrates, or the



1a

Scheme 1. Synthesis of 3-thiocyanatoindole using DEAD and NH_4SCN.

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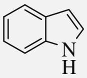
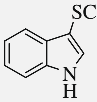
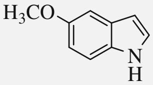
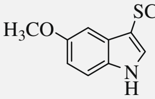
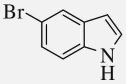
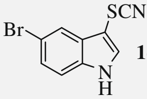
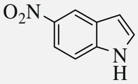
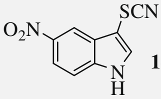
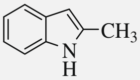
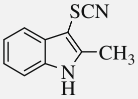
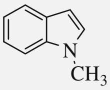
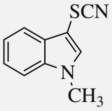
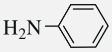
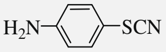
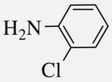
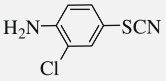
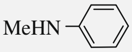
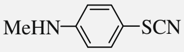
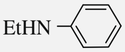
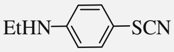
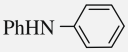
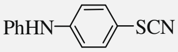
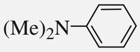
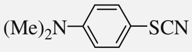
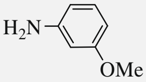
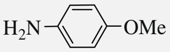
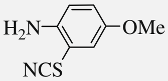
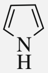
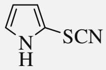
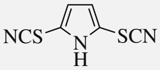
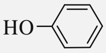
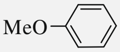
Table 1
Substrate scope in the thiocyanation reaction of arenes using NH_4SCN and DEAD[a]

Entry	Substrate	Product[b]	Yield[c] (%)	Time (min)
1		 **1a**	85[9]	45
2		 **1b**	91[2]	30
3		 **1c**	81[11a]	60
4		 **1d**	80[12]	90
5		 **1e**	79[11a]	45
6		 **1f**	88[11a]	45
7		 **1g**	80[11a]	6
8		 **1h**	75[11a]	150
9		 **1i**	85[11a]	120
10		 **1j**	84[2]	120
11		 **1k**	79[2]	150
12		 **1l**	81[11a]	90
13		–	–	–
14		 **1m**	84[19]	60
15[d]		 **1n**  **1n'**	80[11a]	150
16		–	–	–
17		–	–	–

[a] Molar ratio of arene:DEAD:NH_4SCN was 1:1.8:2.5.
[b] The products were identified from their spectral data and by comparison with known samples.
[c] Isolated yields.
[d] After 15 h, a 15% yield of the bis-adduct was obtained.

assistance of ultrasonic irradiation,[11b] this method is works under milder reaction conditions. A proposed reaction mechanism is shown in Figure 1.

Formation of ammonia and DEAD–H_2 **II** (isolated yield: 71%) accounts for the proposed mechanism. In order to prove the intermediacy of **I** as evidence for this mechanism, the reaction between DEAD and NH_4SCN in dry acetonitrile and in the absence of any amine was studied. Upon mixing these two reagents, the reaction changed color from pale-yellow to dark-orange and product **I** appeared as a precipitate. ^1H and ^{13}C NMR spectroscopy of this precipitate in DMSO-d_6 showed the presence of the NH proton and the N–SCN carbon of **I** at 8.86 and 130.6 ppm, respectively.

To conclude, we have developed an efficient and simple DEAD-mediated thiocyanation of various indoles, anilines and pyrrole

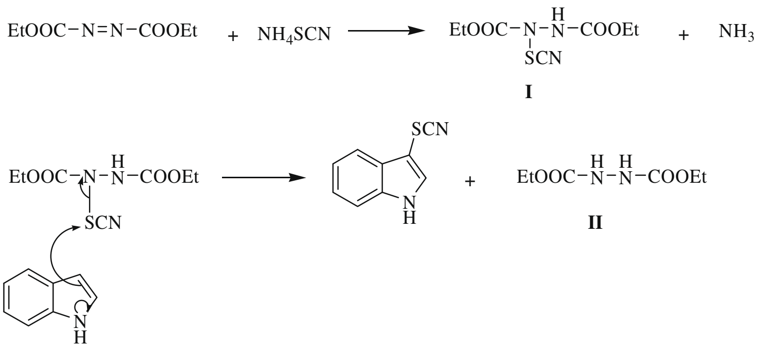


Figure 1. Proposed reaction mechanism.

with high regioselectivity. This method has advantages including mild reaction conditions and clean formation of the desired products in high yields.

Acknowledgment

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18. *Typical procedure for the preparation of* **1a**: indole (1 mmol, 0.117 g) was added to a stirred mixture of NH_4SCN (2.5 mmol, 0.19 g) and DEAD (1.8 mmol, 0.25 mL) in MeCN (3 mL) at room temperature. The progress of the reaction was monitored by TLC, using *n*-hexane/EtOAc (5:1) as eluent. After completion of the reaction, as indicated by TLC, the reaction mixture was concentrated under reduced pressure and the crude product was adsorbed onto silica and purified by flash chromatography on silica gel using *n*-hexane/EtOAc (5:1) to afford 3-thiocyanatoindole (0.148 g, 85%). Mp 70–71 °C;[8] IR (KBr, cm^{-1}): 3315 (NH), 2159 (SCN). ^1H NMR (250 MHz, $CDCl_3$): 8.96 (br s, 1H, NH), 7.81 (1H, d, $J = 9.1$ Hz), 7.43–7.28 (4H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): 136.1, 131.3, 127.7, 123.8, 121.8, 118.6, 112.3, 91.6.
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