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An efficient solvent-free thiocyanation of indoles by grinding

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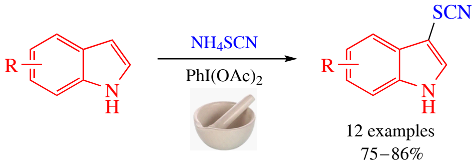
An efficient thiocyanation of indoles by grinding with ammonium thiocyanate and hypervalent iodine reagents under solvent-free conditions has been developed. The reaction proceeded rapidly to provide the target 3-thiocyanatoindoles in 75–86% yields.



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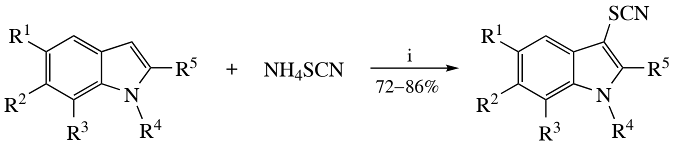
Mechanochemistry, an emerging green chemical synthesis technology, has attracted attention in the past decades. Mechanochemistry relies solely on shear frictional force *via* milling or grinding to achieve efficient chemical transformations.[1] Compared with traditional chemical synthesis, it does not require bulk organic solvents, has shorter reaction times and higher reaction efficiencies, and can achieve certain chemical transformations that are difficult to realize in reaction flasks.[2–4] These features perfectly align with the principles of green chemistry.

Compounds bearing thiocyanato group, particularly the heterocyclic thiocyanates, can be found in natural and bioactive products.[5,6] They also serve as versatile synthetic precursors to other sulfur-containing compounds.[7] Thiocyanation of indoles has received particular attention. Electrophilic thiocyanation strategy is widely employed, and reagents such as *N*-(thiocyanato)dibenzenesulfonimide and *N*-thiocyanatosaccharin have been developed.[8–10] However, these thiocyanating reagents are either expensive or require multiple steps to prepare. Feasible thiocyanation reactions *via* transition metal-catalysis,[11] electrocatalysis,[12] and photocatalysis[13] are limited because they need metal catalysts, bulk organic solvents, long reaction times and have unsatisfactory yields. Recently, Malvestiti[14] reported a mechanochemical electrophilic C–H thiocyanation of arenes in the presence of $(NH_4)_2S_2O_8$ *via* ball milling. Although that procedure was effective for most of the substrates, only 40% yield was obtained for indole. Banerjee[15] reported an efficient mechanochemical synthesis of thiocyanated heterocycles using the combination of NaSCN/*N*-chlorosuccinimide. However, the NaSCN is environmentally unfriendly and an extra milling auxiliary was required to achieve high conversion. In continuation of our interest in thiocyanation reaction,[16] herein we report an efficient solvent-free thiocyanation of indoles with ammonium thiocyanate and $PhI(OAc)_2$ by simple grinding.

Initially, indole **1a** (1 equiv.), NH_4SCN (1.5 equiv.) and $PhI(OAc)_2$ (1.5 equiv.) were grinded in a mortar to optimize the reaction conditions. The reaction proceeded very quickly, the color turned black and acetic acid was smelled after seconds, indicating that a ligand exchange between NH_4SCN and $PhI(OAc)_2$ occurred. TLC analysis showed that indole **1a** was almost completely converted after 15 min and the corresponding thiocyanate product **2a** was isolated in 85% yield (Scheme 1, Table 1, entry 1). Switching the SCN source to NaSCN and KSCN gave slightly lower yields (entries 2 and 3). Reducing the dosage of ammonium thiocyanate led to a decrease in the yield while increasing the dosage to 2 equiv. also did not benefit the reaction (entries 4–6). Inorganic $K_2S_2O_8$ and $Na_2S_2O_8$ were less effective, providing the desired product **2a** in low yields (28 and 33%, respectively, entries 7, 8). Reaction using other hypervalent reagents such as hydroxy(tosyloxy)iodobenzene and bis(trifluoroacetoxy)iodobenzene was also facile, giving **2a** in 76 and 81% yields, respectively (entries 9, 10). All these results indicated that the combination of $PhI(OAc)_2/NH_4SCN$ is a highly active thiocyanating system, which is consistent with other $PhI(OAc)_2$-mediated electrophilic reaction system.[17,18] Thus, the optimized reaction conditions were determined as follows: indole **1a**, NH_4SCN (1.5 equiv.) and $PhI(OAc)_2$ (1.5 equiv.), grinding for 15 min.



1a–n **2a–n**

a $R^1 = R^2 = R^3 = R^4 = R^5 = H$
b $R^1 = MeO, R^2 = R^3 = R^4 = R^5 = H$
c $R^1 = Cl, R^2 = R^3 = R^4 = R^5 = H$
d $R^1 = Br, R^2 = R^3 = R^4 = R^5 = H$
e $R^1 = CO_2Me, R^2 = R^3 = R^4 = R^5 = H$
f $R^1 = CN, R^2 = R^3 = R^4 = R^5 = H$
g $R^1 = NO_2, R^2 = R^3 = R^4 = R^5 = H$
h $R^1 = CO_2H, R^2 = R^3 = R^4 = R^5 = H$
i $R^1 = R^3 = R^4 = R^5 = H, R^2 = Cl$
j $R^1 = R^2 = R^4 = R^5 = H, R^3 = Me$
k $R^1 = R^2 = R^3 = R^4 = H, R^5 = Me$
l $R^1 = R^2 = R^3 = R^4 = H, R^5 = Ph$
m $R^1 = Cl, R^2 = R^3 = R^4 = H, R^5 = Me$
n $R^1 = R^2 = R^3 = R^5 = H, R^4 = Me$

Scheme 1 *Reagents and optimized conditions*: i, indole **1** (1 mmol), ammonium thiocyanate (1.5 mmol), $PhI(OAc)_2$ (1.5 mmol), grinding for 15 min.

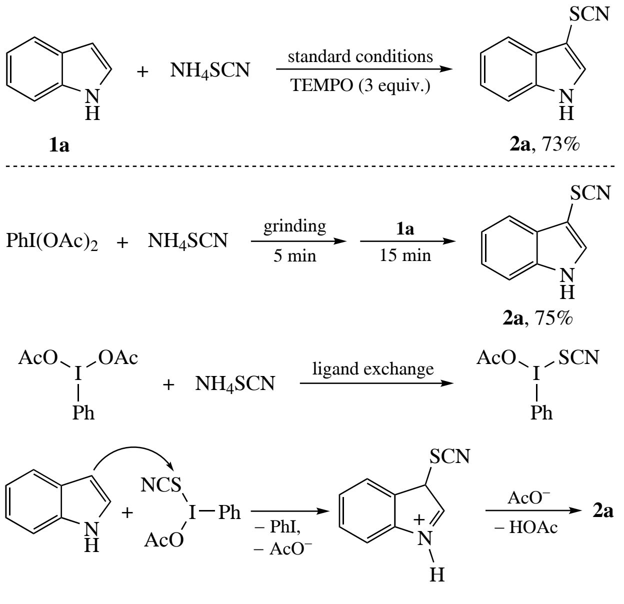
Table 1 Optimization of reaction conditions for thiocyanation of indole **1a**.[a]

Entry	[SCN] source	[SCN] loading (equiv.)	Oxidant	Yield of **2a** (%)[b]
1	NH_4SCN	1.5	$PhI(OAc)_2$	85
2	NaSCN	1.5	$PhI(OAc)_2$	80
3	KSCN	1.5	$PhI(OAc)_2$	77
4	NH_4SCN	1.2	$PhI(OAc)_2$	71
5	NH_4SCN	1.0	$PhI(OAc)_2$	63
6	NH_4SCN	2.0	$PhI(OAc)_2$	83
7	NH_4SCN	1.5	$K_2S_2O_8$	28
8	NH_4SCN	1.5	$Na_2S_2O_8$	33
9	NH_4SCN	1.5	PhI(OH)(OTs)	76
10	NH_4SCN	1.5	$PhI[OC(O)CF_3]_2$	81
11	NH_4SCN	1.5	$PhI(OAc)_2$ + TEMPO[c]	73
12[d]	NH_4SCN	1.5	$PhI(OAc)_2$	75

[a] *Reaction conditions*: indole **1a** (1 mmol, 1 equiv.), thiocyanate, oxidant (1.5 equiv.), room temperature, grinding, 15 min. [b] Isolated yield. [c] 3 equiv. of TEMPO. [d] NH_4SCN and $PhI(OAc)_2$ were grinded for 5 min, then **2a** was added, and grinding was performed for 15 min.

With the optimized reaction conditions in hand, a series of indoles **1a–n** were examined (see Scheme 1).[†] Indoles with such functional groups as methyl, methoxy, halogeno, cyano, methoxycarbonyl, and carboxy at different positions of the benzene ring underwent the reaction smoothly to afford the corresponding products in good yields (75–86%). Generally, indoles bearing electron-withdrawing groups provided relative lower yields. A scale-up experiment was then carried out with indole **1a** (0.584 g, 5 mmol), and NH_4SCN (0.57 g, 7.5 mmol). Pleasingly, the reaction also proceeded rapidly and 0.76 g (88%) of product **2a** was obtained.

Some control experiments were carried out. A 73% yield of product **2a** was obtained in the presence of 3 equiv. of the radical scavenger, 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), indicating that the radical pathway could be ruled out (Scheme 2, Table 1, entry 11). Moreover, when the mixture of $PhI(OAc)_2$ and NH_4SCN was ground for 5 min, acetic acid was liberated during the process. After addition of indole **1a**, the mixture was kept grinding for another 15 min, and the desired product **2a** was isolated in 75% yield (entry 12). Based on the above results, a mechanism is proposed (see Scheme 2). Initially, a ligand exchange occurred between $PhI(OAc)_2$ and NH_4SCN to give [acetoxy(thiocyanato)iodo]benzene PhI(OAc)SCN. This *in situ* generated electrophilic thiocyanating reagent was then attacked by indole to provide product **2a**.



Scheme 2

In summary, an efficient electrophilic thiocyanation of indoles *via* simple grinding has been developed. All the starting materials are cheap and stable. No metal catalysts, solvents and additives are required. The reaction conditions are green and mild, providing the thiocyanated indoles in good yields in short reaction times.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7677.

[†] *General procedure for the synthesis of* **2a–n**. The mixture of indole **1** (1 mmol), ammonium thiocyanate (1.5 mmol, 114 mg) and $PhI(OAc)_2$ (1.5 mmol, 483 mg) was ground in a mortar with a pestle. The reaction was kept grinding until the starting materials disappeared (monitored by TLC, *ca.* 15 min). The residue was then extracted with ethyl acetate and washed with water. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (light petroleum/ethyl acetate, 10 : 1, v/v) to afford the pure desired product.

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