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EFFICIENT THIOCYANATION OF INDOLES USING *PARA*-TOLUENE SULFONIC ACID

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Treatment of indoles with ammonium thiocyanate in the presence of para-toluene sulfonic acid afforded the corresponding 3-thiocyano indoles at room temperature in excellent yields.

Keywords: Ammonium thiocyanate; indoles; *para*-toluene sulfonic acid; regioselectivity; thiocyanation

INTRODUCTION

Thiocyanation of aromatic and heteroaromatic compounds is a useful reaction in organic synthesis because this reaction initiates the direct introduction of sulfur into the molecules.[1,2] Aryl and heteroaryl thiocyanates are important intermediates for the synthesis of sulfur-containing heterocycles.[3] The thiocyanate group can also be converted into other sulfur-bearing groups.[4,5] Aryl thiocyanates have been prepared earlier using different reagents under various conditions.[1–7] However, only a limited number of reagents [such as *N*-halosuccinamides (*N*-chlorosuccinimide, NCS and N-bromosuccinimide, NBS), ceric ammonium nitrate (CAN), K10 clay, oxone, and halogens (Br_2 and I_2)] have been reported for thiocyanation of indoles.[8–12] Many of the methods utilizing these reagents suffer from various drawbacks such as the use of excess amounts of strong oxiding agents and toxic metal thiocyanates, unsatisfactory yields, and high temperatures.

RESULTS AND DISCUSSION

In continuation of our work[13–16] on the development of useful synthetic methodologies, we observed that the thiocyanation of indoles can efficiently be carried out by treatment with ammonium thiocyanate in the presence of *para*-tolune sulfonic acid (*p*-TSA) at room temperature (Scheme 1).

Various indoles were converted into the corresponding 3-thiocyano analogs by following this method (Table 1). The derivatives of indoles with substituents in the

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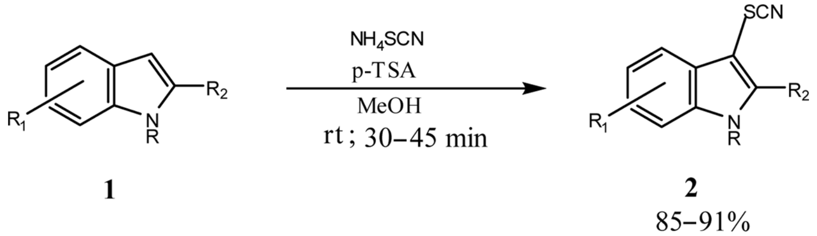


Scheme 1. Thiocyanation of indoles using *para*-toluene sulfonic acid.

aromatic ring as well as 2-methyl indole and *N*-methyl indole were applied equally. In each case, only the monothiocyanation product was formed. The reaction was completed within 30–45 min, and the yields were good (85–91%). Indoles containing electron-donating as well as electron-withdrawing groups smoothly underwent the conversion. The reaction is highly regioselective, forming 3-thiocyano derivaties as the products. The structures of the thiocyanates were established from their spectral [infrared (IR), ^{1}H NMR, and mass (MS)] and analytical data.

CONCLUSION

In conclusion, we have developed a simple and efficient method for high-yielding regioselective thiocyanation of indoles by treatment with ammonium thiocyanate using *para*-tolune sulfonic acid at room temperature.

EXPERIMENTAL

General Procedure for the Synthesis of β-Amino Ketones

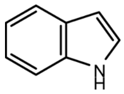
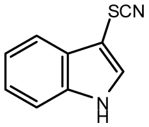
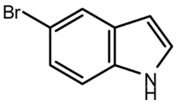
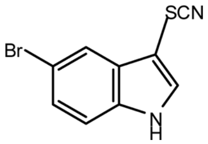
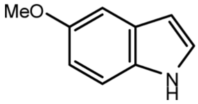
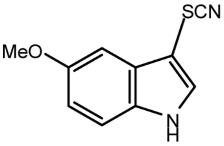
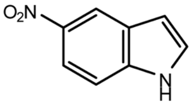
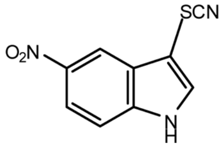
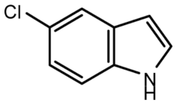
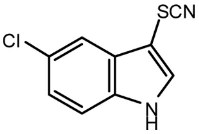
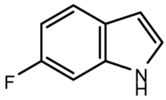
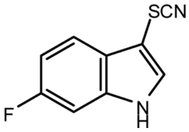
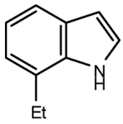
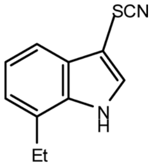
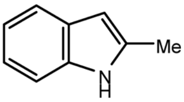
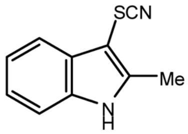
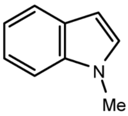
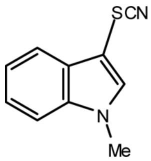
p-TSA (0.2 mmol) was added to a solution of indole (1 mmol) and NH_4SCN (1.6 mmol) in methanol (MeOH, 5 mL), and the mixture was stirred at room temperature. The reaction was monitored by thin-layer cromotography (TLC). After completion, the reaction was quenched with aqueous saturated $NaHCO_3$ solution, and the mixture was extracted with EtOAc (3 × 10 mL). The extract was concentrated, and the residue was purified by column chromatography (silica gel, hexane–EtOAc) to obtain pure thiocyanate.

The spectroscopic (^{1}H NMR and MS) and analytical data of the new compounds are given here.

Compound 2e (Table 1)

IR (KBr): υ_{max} 3414, 2155, 1647, 1457 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.82 (1H, brs), 7.64 (2H, brs), 7.43 (1H, d, $J = 8.0$ Hz), 7.20 (1H, dd, $J = 8.0$ Hz); ESI-MS: m/z 231, 233 $[M + Na]^+$. Anal. calcd. for $C_9H_5ClN_2S$: C, 51.80; H, 2.40; N, 13.43%. Found: C, 51.68; H, 2.49; N, 13.36%.

Table 1. Synthesis of 3-thiocyano indoles using *p*-TSA[a]

No.	Indole **1**	Product **2**	Time (min)	Isolated yield (%)
a			45	88
b			40	86
c			40	87
d			40	87
e			40	91
f			45	89
g			30	86
h			30	85
i			40	88

[a]The structures of the products were settled from their spectral (IR, ^{1}H NMR, and MS) data.

Compound 2f (Table 1)

IR (KBr): υ_{max} 3348, 2158, 1631, 1511, 1449 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz): δ 8.62 (1H, brs), 7.65 (1H, m), 7.48 (1H, d, $J = 1.5$ Hz), 7.14–7.01 (2H, m); ESI-MS: m/z 215 $[M + Na]^+$. Anal. calcd. for $C_9H_5FN_2S$: C, 56.25; H, 2.60; N, 14.58%. Found: C, 56.32; H, 2.54; N, 14.51%.

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