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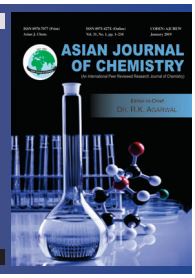

Triton-B Catalyzed One Pot Multicomponent Synthesis of Isothiocyanates in Non-Aqueous Medium

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A facile and novel method to synthesize isothiocyanides from cyclic and acyclic amines and carbon disulphide in DMSO with Triton-B as catalyst in non-aqueous medium is being reported. The method is less tedious and offers excellent yields. The structures have been elucidated by ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

Keywords: Isothiocyanates, Carbon disulphide, Amines, Triton-B.

INTRODUCTION

Isothiocyanates are a group of vital class of compounds utilized in natural products, synthetic and medicinal fields as antimicrobial [1,2], antitumor [3-6], antiproliferatives [7], enzyme inhibitors for the HIV virus [8,9] and other biological assays of DNA and protein [10-12]. Isothiocyanates are also used as effective synthetic intermediates in nucleophilic addition and cycloaddition reactions. They are used as starting materials of sulphur and nitrogen containing organic compounds with biological activities. Due to strong electron withdrawing substituent, they are used popularly used as agrochemicals and pharmaceuticals [13-17]. Isothiocyanates are important precursors for the construction of pharmaceutically important heterocycles and are frequently encountered in many natural products [18-31].

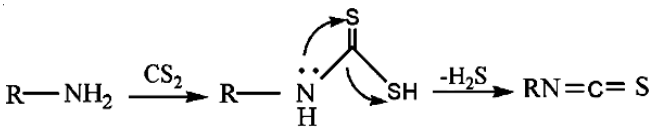
Isothiocyanates are prepared from amines by treatment with carbon disulphide, ammonia and lead nitrate [32]. The most conventional method remains the treatment with thiophosgene [33]. Isothiocyanates have been also reported to be prepared by monoarylisothioureas [34], phosphoramidates [35], iminodithiazoles [36], tertiary alcohols [37-39], amines [40-46], nitrile oxides [47-49], isocyanides [50-52], isocyanates [53], by decomposition of dithiocarbamates [54], dithiocarbamic acid [55], peptide coupling reagents [56], di-*tert*-butyldicarbonate [57], *bis*-(trichloromethyl)carbonate (BTC) [58], *etc*. However, most of these methods offer low yields, inconvenient workup procedures, poor stability, expensive catalysts and use of highly toxic reagents. Also, recycling remains the major setback. Thus there remain still the need to develop better methods by searching novel reagents and catalytic system.

Our work is focussed on development of novel and efficient synthetic methodologies for synthesis of cyclic and acyclic isothiocyanates through *in situ* employment of carbon disulphide in presence of a phase transfer catalyst Triton-B, by reacting aliphatic and cyclic amines at room temperature.

EXPERIMENTAL

All the chemicals were procured by Merck, Aldrich and Fluka chemical companies and used without further purification. Identification of products was done by comparing their physical data and spectral data with the already known compounds. Infrared spectra were analyzed on a Bomen MB-FTIR spectrophotometer while NMR spectra were recorded on Bruker Advance DPX instrument spectrophotometer (400 MHz) using $CDCl_3$ as solvent and tetramethysilane as standard. Elemental analysis was carried out by Carlo-Erba EA 1110 CHNOS analyzer. Mass spectra were recorded using a Bruker Esquire 3000 spectrometer.

General procedure: To a solution of amines (1 mmol) in DMSO, added carbon disulphide under nitrogen atmosphere and stirred for 15 min to afford compound **2**. Further added triton-B after reaction mixture was stirred for 2 h to afford compound **3** (**Scheme-I**). After completion, extracted with ethyl acetate to yield isothiocyanates upto 80-99 %.



R = C_6H_5 (**1**); C_2H_4Cl (**2**); C_7H_7 (**3**); $C_6H_4NO_2$ (**4**); C_5H_4N (**5**); C_6H_{11} (**6**); C_7H_5O (**7**); C_6H_4F (**8**);

Scheme-I: Synthesis of isothiocyantaes from corresponding amines (reagents and conditions DMSO (anhyd.), Triton-B, CS_2, 2-4 h)

The synthesized trithiocarbonates was subjected to ^1H NMR, ^{13}C NMR and mass spectroscopy for structure elucidation. The novel one pot synthesis yields good to excellent amount of isothiocyanates, both cyclic and acyclic substituent at room temperature.

Isothiocyanatobenzene (1): Yield: 96 %; yellow oily liquid. ^1H NMR ($CDCl_3$): δ 7.37-7.33 (m, 2H), 7.30-7.27 (m, 1H), 7.23-7.21 (m, 2H); MS (*m/z*): 135. Anal. calcd. (found) % for C_7H_5NS: C, 62.19; H, 3.73; N, 10.36; S, 23.72.

1-Chloro-2-isothiocyanatoethane (2): Yield: 94 %; yellow oily liquid. ^1H NMR ($CDCl_3$): δ 3.830 (t, *J* = 6.0 Hz, 2H), 3.69 (t, *J* = 6.0 Hz, 2H); MS (*m/z*): 121.5. Anal. calcd. (found) % for C_3H_4NSCl: C, 29.63; H, 3.32; Cl, 29.16; N, 11.52; S, 26.37.

Isothiocyanatomethylbenzene (3): Yield: 97 %; yellow oily liquid. ^1H NMR ($CDCl_3$): δ 7.42-7.31 (m, 5H), 4.72 (s, 2H); MS (*m/z*):149. Anal. calcd. (found) % for C_8H_7NS: C, 64.39; H, 4.73; N, 9.39; S, 21.49.

1-Isothiocyanato-4-nitrobenzene (4): Yield: 94 %; yellow oily liquid. ^1H NMR ($CDCl_3$): δ 8.26-8.22 (m, 2H), 7.36-7.33 (m, 2H); MS (*m/z*): 180. Anal. calcd. (found) % for $C_7H_4N_2O_2S$: C, 46.66; H, 2.24; N, 15.55; O, 17.76; S, 17.80.

3-Isothiocyanatopyridine (5): Yield: 97 %; yellow oily liquid. ^1H NMR ($CDCl_3$): δ 8.53 (s, 1H), 8.49 (d, *J* = 6.0 Hz, 1H), 7.52-7.49 (m, 1H), 7.31-3.28 (m, 1H); MS (*m/z*): 138. Anal. calcd. (found) % for $C_6H_4N_2S$: C, 52.92; H, 2.96; N, 20.57; S, 23.55.

Isothiocyanatocyclohexane (6): Yield: 95 %; yellow oily liquid. ^1H NMR ($CDCl_3$): δ 3.71-3.66 (m, 1H), 1.89-1.87 (m, 2H), 1.75-1.61 (m, 4H), 1.54-1.42 (m, 1H), 1.40-1.37 (m, 3H); MS (*m/z*): 141. Anal. calcd. (found) % for $C_7H_{11}NS$: C, 59.53; H, 7.85; N, 9.92; S, 22.70.

Benzoyl isothiocyanate (7): Yield: 94 %; yellow oily liquid. ^1H NMR ($CDCl_3$): δ 7.89-7.82 (m,1H), 7.81-7.83 (m, 1H), 7.63-7.57 (m, 1H), 7.55-7.51 (m, 1H), 7.49-7.46 (m, 1H); MS (*m/z*): 163. Anal. calcd. (found) % for C_8H_5NOS: C, 58.88; H, 3.09; N, 8.58; O, 9.80; S, 19.65.

1-Fluoro-2-isothiocyanatobenzene (8): Yield: 97 %; yellow oily liquid. ^1H NMR ($CDCl_3$): δ 7.24-7.219 (m,1H), 7.20-7.19 (m, 1H), 7.18-7.16 (m, 1H), 7.14-7.10 (m, 2H); MS (*m/z*): 153. Anal. calcd. (found) % for C_7H_4NSF: C, 54.89; H, 2.63; F, 12.40; N, 9.14; S, 20.93.

RESULTS AND DISCUSSION

The synthesis of isothiocyanates is afforded by reacting primary, secondary and tertiary amines in DMSO in carbon disulphide environment in presence of Triton-B, a phase transfer catalyst at room temperature for 2-4 h to afford trithiocarbonates in a very good to excellent yields (80-99 %).

Several solvents like dimethyl sulphoxide, *N*,*N*-dimethyl formamide, benzene, acetonitrile, dichloromethane, hexane, heptanes, methanol, chloroform and acetone were examined and found that dimethyl sulphoxide (DMSO) proved to be the most suitable solvent for carrying out the transformation.

Conclusion

In conclusion, a convenient and efficient protocol is developed for the one pot two component coupling of a range of primary, secondary and tertiary range amines *via* combination of Triton-B and carbon disulphide. This reaction generates corresponding isothiocyanates in excellent yields (80-99 %) at the room temperature. Furthermore, this method offers substrate versatility, good selectivity, high yields, high efficiency, excellent functional group compatibility, operational simplicity, inexpensive catalyst, easily available reagents and mild reaction conditions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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