

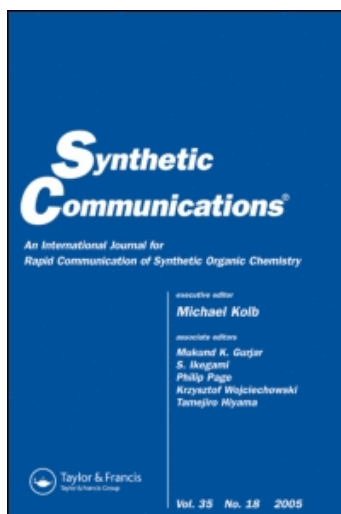
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EFFICIENT PREPARATION OF ISOTHIOCYANATES FROM DITHIOCARBAMATES USING BROMINELESS BROMINATING REAGENT

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For the first time, the crystal structure of a ditribromide reagent 1,1'-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT) has been determined. Utilizing this thiophilic bromineless brominating agent EDPBT, highly useful synthetic intermediates (alkyl and aryl isothiocyanates) have been achieved directly from dithiocarbamates. EDPBT can be easily prepared from readily available reagents. It has been used as a thiophilic reagent, and its thiophilicity dominates over its brominating ability for substrates amenable to bromination. This is a sustainable process for the preparation of isothiocyanates because the spent reagent can be recovered, regenerated, and reused.

Keywords: Desulfurizing agent; dithiocarbamate; ditribromide; isothiocyanate

INTRODUCTION

A hypervalent iodine reagent, diacetoxyiodobenzene (DIB), has been reported to be an efficient thiophilic and desulfurizing agent, which has been employed for the oxidative N-acylation of 1,3-disubstituted thiourea,^[1] in the preparation of isothiocyanates from dithiocarbamates, and for the construction of various heterocycles by a desulfurization strategy.^[2] In spite of the superiority of the method, the expensive nature of the hypervalent iodine reagent is the major impediment for large scale requirements. Further, we have demonstrated that the hypervalency of iodine is not really essential for the transformation of dithiocarbamate to isothiocyanates and that other thiophilic halogens such as molecular iodine can serve the purpose.^[3] We were inquisitive to know whether other halogens such as bromine or its equivalents (tribromides) could be employed for this purpose. Handling of molecular bromine is cumbersome because of its hazardous nature, and thus special care is required for its use, storage, and transport. To overcome this problem, several bromineless brominating reagents have been prepared.^[4] However, they are associated with certain drawbacks such as phase-transfer property and poor

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stability, and recycling of the spent reagent is the major setback, thereby making the overall process expensive. We have recently designed a ditribromide reagent, 1,2-dipyridiniumditribromide-ethane or 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT), which is superior to all known tribromides and have several advantages over molecular bromine and other tribromides.^[5] This reagent has been utilized as catalyst and reagent for acylation of alcohols,^[6a] regioselective enolate addition to 9-phenyl-9H-xanthene-9-ol,^[6b,c] synthesis of various thiazolidene-2-imine derivatives,^[6d-f] synthesis of 1,4-dithiins and 1,4-benzodithiins,^[6g] construction of 1,3-oxathiolan-2-ylidenes,^[6h] and conversion of urazole to triazonediones.^[6i]

Isothiocyanates are important precursors for the construction of pharmaceutically important heterocycles and are frequently encountered in many natural products.^[7] Because of their unique reactivity toward –OH and –NH₂ nucleophiles present in nucleic acids and proteins, they serve as chemoselective electrophiles in bioconjugate and neoglycoconjugate chemistry, particularly for biological assays.^[8] The conventional method for the preparation of isothiocyanate involves the reaction of deadly toxic thiophosgene with amine.^[9] High toxicity of thiophosgene, difficulties in handling, and incompatibility with many functional groups has led to the development of many of its synthetic equivalents,^[10] and the thiocarbonyl transfer reagents are a case in point.^[11] In addition, they are also prepared by decomposition of dithiocarbamates with diverse reagents such as uranium- and phosphonium-based coupling agents,^[12] tosylchloride,^[13] di-*tert*-butyl dicarbonate,^[14] hydrogen peroxide,^[15] and ethylchlorocarbonate.^[16]

Thus, preparation of this synthetically useful intermediate isothiocyanate involves extremely arduous reaction conditions, toxic and expensive reagents, and high reaction temperatures, gives poor yields, and requires tedious purification procedures. Taking cues from the thiophilic and desulfurizing ability of hypervalent iodine and molecular iodine, we wondered if the same could be achieved with other halogens, particularly bromine or its equivalent such as 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT).^[5] In this article, we report bromineless bromine-mediated preparation of organic isothiocyanates from corresponding dithiocarbamates.

RESULTS AND DISCUSSION

It is essential to understand the remarkable stability of 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) reagent through an x-ray crystallographic structural analysis (given in the Experimental section). Although the crystal structure of several inorganic tribromides are known, structures of only few organic ammonium tribromides have been reported.^[17] All the reported organic ammonium tribromides are in 1:1 stoichiometry with respect to cations and are nearly linear molecules. To reconfirm the stoichiometry and investigate factors that control the intramolecular interactions over the crystal engineering, the x-ray crystal structure of 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) was determined. It crystallized in the space group monoclinic P2(1)/c. The ORTEP (Oak Ridge Thermal Ellipsoid Program) diagram with atomic numbering scheme is shown in Fig. 1. In the asymmetric unit, only one half of the molecule is present. A unit cell representation is shown in Fig. 2.

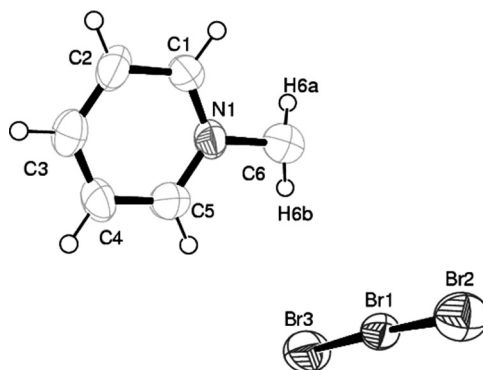


Figure 1. ORTEP view with atomic numbering scheme of EDPBT.

The two pyridinium rings are nearly planar and are parallel to each other. Each tribromide is nearly linear with a bond angle of 176.82° between Br2–Br1–Br3. Pointing away from each other, tribromides are held parallel in the opposite faces of the bispyridyl moiety (Figs. 2 and 3). The linear tribromide is not symmetrically placed to the pyridine nitrogen atoms of the bispyridyl moiety. One of the terminal bromine atoms (Br3) of the tribromide is closer to one of the nitrogen atoms, which is at a distance of 4.157 \AA , and the distance with respect to other nitrogen is 4.255 \AA . From one face of the molecule (Br3), three intermolecular C–H...Br interactions form with H1 of one pyridyl, H5 of the other pyridyl, and the bridging methylene H6A and also intramolecularly with H2 of the adjacent molecule, whereas the central bromine (Br1) atom with CH...Br contacts intramolecularly with H6A and intermolecularly with H4 of the adjacent molecule. The other terminal bromine atom (Br2) forms only intramolecular CH...Br interactions with the methylene hydrogen H6B of adjacent molecule. The same interaction occurs from the other face of the molecule, which contributes to the crystal packing (Fig. 3).

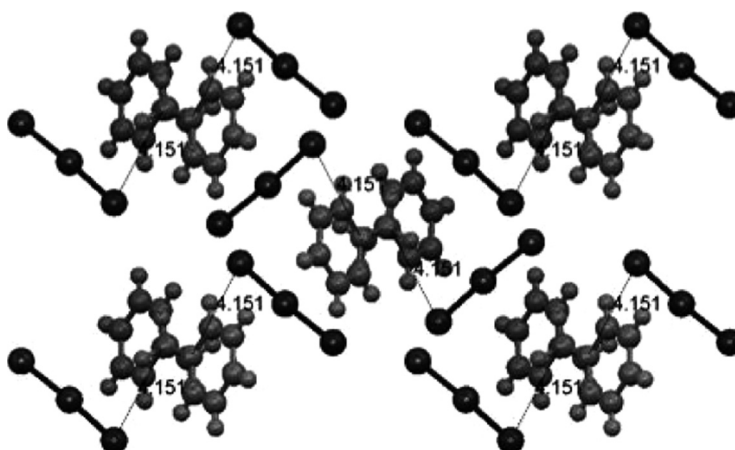


Figure 2. Unit cell representation of EDPBT.

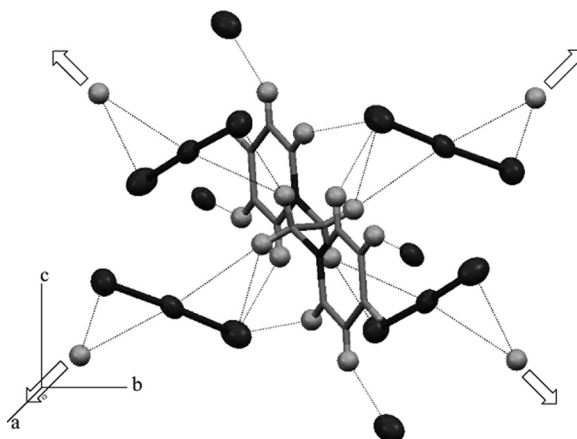


Figure 3. Inter- and intramolecular CH...Br interactions.

As shown in Figs. 3 and 4, the crystal-packing diagrams are quite fascinating. The crystal packing comprises two different layers growing in opposite directions, each held by π - π stacking interactions as viewed from projection along the c axis (Fig. 4). The perpendicular intermolecular distance between the planes of one of the pyridine molecule to that of neighboring molecules is estimated to be 3.651 Å, suggesting the existence of noncovalent π - π interactions. The clear π - π interactions between the molecules nearby play an important role in guiding the compound EDPBT to an extremely ordered crystal packing and hence the remarkable stability of the compound as compared to simple pyridinium tribromide, which is not so stable and is reported to have a different bromine composition with different melting points.

Having understood the exceptional stability of EDPBT, we explored its thiophilic property for synthetically useful transformations. The thiophilicity of bromine

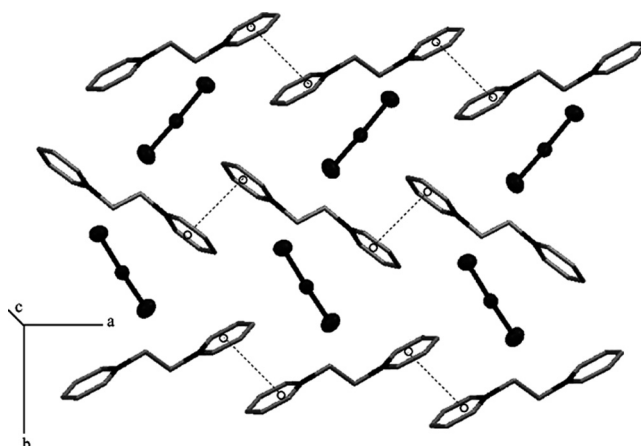
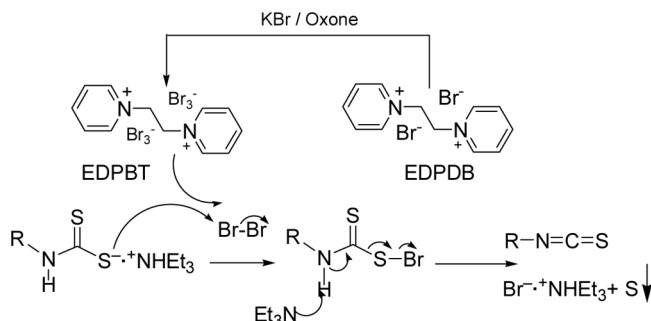


Figure 4. The π - π stacking interactions of EDPBT. Hydrogen atoms are omitted for clarity.



Scheme 1. Proposed reaction mechanism of formation of isothiocyanate.

is expected to be similar to that of molecular iodine and hypervalent iodine. When dithiocarbamate **1** (1 mmol) was treated with EDPBT (0.5 mmol) in the presence of triethylamine (2 mmol) in acetonitrile, isothiocyanate **1a** was obtained in nearly quantitative yields (96% after purification). Triethylamine is sufficiently basic (pK_a 10.78) compared to aromatic amines **1–10** (pK_a 2.46–5.63), aliphatic and benzylic amines **11–17** (pK_a 9.33–10.77), and the acidity of the dithiocarbamate-bound NH proton was expected to increase upon salt formation. The proposed reaction mechanism for the formation of isothiocyanate is shown in Scheme 1. This reaction is associated with the formation of elemental sulfur, which supports the mechanism.

The consumed EDPDB quantitatively precipitated out from the reaction medium (CH_3CN solvent), leaving the products and other by-products soluble in acetonitrile. Quantitative recovery of the spent reagent can be achieved by filtration. The isolated spent reagent can be recycled by the addition of requisite amount of KBr and Oxone.^[5] The mother liquor containing isothiocyanate was evaporated and mixed with water, and the desired isothiocyanate was extracted with hexane. Further purification was achieved by passing it through a short column of silica gel.

The scope of this interesting transformation with different substituted aryl dithiocarbamates was evaluated (Table 1). In general, all the reactions were very clean, and the isothiocyanates were obtained in excellent yields under the optimized reaction conditions. The yields obtained are almost comparable to the yield obtained using diacetoxyiodobenzene (DIB) and molecular iodine.^[2a,3]

Substrates containing fluoro (**2**) and chloro (**3**, **4**, and **6**) substituents gave their corresponding isothiocyanates **2a**, **3a**, **4a**, and **6a**, respectively, in excellent yields. Deactivating the substrate with nitro functionality (**5**) efficiently yielded the corresponding isothiocyanate (**6**). Activated substrates **7** and **8** are usually prone to ring bromination with EDPBT.^[5] However, in these cases, its thiophilicity seems to be predominate over its brominating ability as demonstrated by the isolation of exclusive isothiocyanates **7a** and **8a** without any traces of brominated products. The deactivated substrate with carbonyl functionality (**9**) furnished its isothiocyanate (**9a**) without undergoing α -bromination. Hindered and disubstituted dithiocarbamate (**10**) efficiently gave isothiocyanate (**10a**) in excellent yields. *o*-Iodoisothiocyanates are useful precursors for the construction of various heterocycles.^[18]

As shown in Table 2, dithiocarbamates of aliphatic amines (**11** and **12**) and benzylic amines (**13** and **14**) gave their isothiocyanates in good yields. Dithiocarbamate

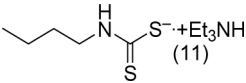
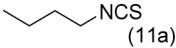
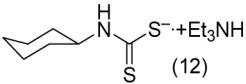
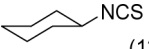
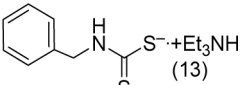
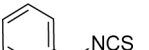
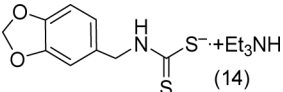
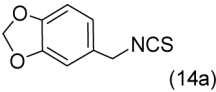
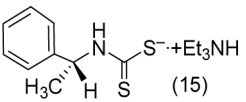
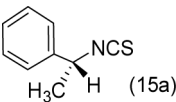
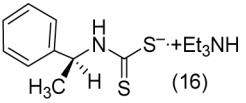
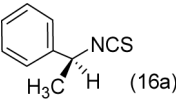
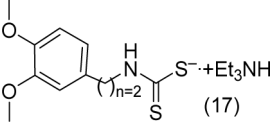
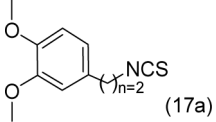
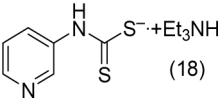
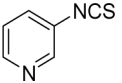
Table 1. Preparation of isothiocyanates from dithiocarbamates and EDPBT^a

Substrate	Product ^b	Yield (%) ^c [Ref.]
		96 ^[3]
		85 ^[3]
		95 ^[3]
		96 ^[3]
		95 ^[3]
		92 ^[3]
		91 ^[13]
		94 ^[3]
		88 ^[23]
		95

^aReactions were monitored by TLC.^bConfirmed by IR, ¹H NMR, and ¹³C NMR.^cIsolated yield.

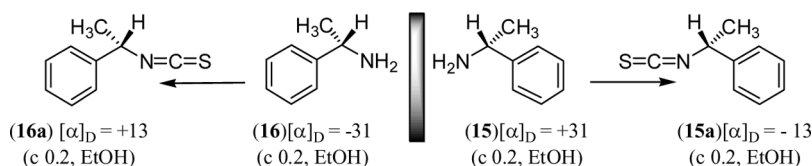
salts derived from chiral amines (**15** and **16**) resulted in their isothiocyanates **15a** and **16a** in excellent yields with retention of optical activity, as shown in Scheme 2. The dextrorotatory R-(+)- α -methylbenzylamine (**15**) gave levorotatory R-(-)- α -methylbenzylisothiocyanate (**15a**), where as the levorotatory

Table 2. Preparation of isothiocyanates from dithiocarbamates and EDPBT^a

Substrate	Product ^b	Yield (%) ^c [Ref.]
	 (11a)	70 ^[3]
	 (12a)	85 ^[3]
	 (13a)	96 ^[3]
	 (14a)	93
	 (15a)	92 ^[24a,b]
	 (16a)	93 ^[24b]
	 (17a)	75
	 (18a)	83 ^[25]

^aReactions were monitored by TLC.^bConfirmed by IR, ¹H NMR, and ¹³C NMR.^cIsolated yield.

S-(−)-α-methylbenzylamine (**16**) gave dextrorotatory S-(+)-α-methylbenzylisothiocyanate (**16a**). As expected, the specific rotation for R-(−)-α-methylbenzylisothiocyanate (**15a**) is equal and opposite of its enantiomer S-(+)-α-methylbenzylisothiocyanate (**16a**) (Scheme 2).

**Scheme 2.** Specific rotations of chiral amines and their isothiocyanates.

Isothiocyanate of homoveratrylamine (**17a**) was obtained successfully in good yield from its dithiocarbamate salt (**17**). 4-Pyridyl isothiocyanate was found to be too unstable to isolate by this method, an observation consistent with others.^[19] However, 3-pyridyl isothiocyanate (**18a**) could be synthesized in excellent yields from its dithiocarbamate salt (**18**).

CONCLUSION

In conclusion, we have reported the x-ray crystal structure of a ditribromide reagent 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT), which helps in understanding its stability and reactivity. For the first time, this bromineless brominating reagent has been used as a thiophilic reagent for sustainable preparation of both alky and aryl isothiocyanates from dithiocarbamate salts. The ease of preparation of this reagent, facile isolation of products, and recyclability of spent reagent make these methods environmentally acceptable.

EXPERIMENTAL

General Information

All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh) was used for the column chromatography. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60F₂₅₄(0.25 mm). NMR spectra were recorded in CDCl₃ or dimethylsulfoxide (DMSO-d₆) with tetramethylsilane (TMS) as the internal standard for ¹H NMR (400 MHz) CDCl₃ and DMSO-d₆ solvent as the internal standard for ¹³C NMR (100 MHz). Mass spectra were recorded using a Waters mass spectrometry (MS) system, Q-TOF premier, and data were analyzed using Mass Lynx 4.1. Specific rotations were recorded on a Perkin-Elmer model 343 polarimeter. Elemental analysis was performed with a Perkin-Elmer 2400 elemental analyzer. Melting points were recorded on a Buchi B-545 melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer.

Typical Experimental Procedure

EDPBT (0.666 g, 1 mmol) was added to a stirred suspension of dithiocarbamate salt **1** (0.542 g, 2 mmol) in acetonitrile (8 mL) containing triethylamine (0.556 μL, 4 mmol) pinch by pinch over a period of 10 min under ice-cold conditions. After completion of the reaction, as judged from TLC, the reaction mixture was allowed to stand, and the precipitated spent reagent was filtered, washed with acetonitrile (2 × 1 mL), and kept aside for recycling. Acetonitrile was evaporated and admixed with water (10 mL), and the product was extracted with hexane (2 × 10 mL). The hexane layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure, and purified over a short column of silica gel (100% hexane) to give

259 mg (96% yield) of **1a**.^[3] Oily liquid; ¹H NMR (400 MHz, CDCl₃): 7.21–7.37 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): 125.8, 127.4, 129.6, 131.3, 135.3. IR (KBr, cm⁻¹): 3064, 2164, 2063, 1591, 1489, 1474, 1451, 1070, 927, 905, 749, 684 cm⁻¹. C₇H₅NS (135.19): calcd. C, 62.19; H, 3.72; N, 10.36; S, 23.72. Found: C, 62.12; H, 3.66; N, 10.45; S, 23.62.

Crystallographic Description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoK α radiation ($\lambda = 0.71073 \text{ \AA}$) at 298 K. Cell parameters were retrieved using SMART^[20] software and refined with SAINT^[20] on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS.^[21] The structure was solved by direct methods implemented in SHELX-97^[22] program and refined by full-matrix least-squares methods on F². All nonhydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. Orange crystals were isolated in rectangular shapes from acetonitrile at room temperature.

Crystallographic description of EDPBT. Crystal dimension (mm): $0.48 \times 0.28 \times 0.19$; C₁₂H₁₄Br₆N₂, M_r = 665.71; monoclinic, space group *P2(1)/c*; $a = 8.3171(7) \text{ \AA}$, $b = 13.7174(11) \text{ \AA}$, $c = 8.6130(7) \text{ \AA}$; $\alpha = \gamma = 90^\circ$, $\beta = 108.025(4)^\circ$, $V = 934.42(13) \text{ \AA}^3$; $Z = 2$; $\rho_{\text{cal}} = 2.366 \text{ mg/m}^3$; $\mu (\text{mm}^{-1}) = 12.882$; $F(000) = 620$; reflection collected/unique = 7461/2820; refinement method = full-matrix least-squares on F^2 ; final R indices [$I > 2\sigma$] $R_1 = 0.0392$, $wR_2 = 0.0898$, R indices (all data) $R_1 = 0.0795$, $wR_2 = 0.1027$; goodness of fit = 1.013. CCDC No. 718734.

Spectral Data

The new compounds were fully characterized by IR, NMR (¹H, ¹³C), MS, and elemental analysis.

2-Iodo-1-isothiocyanato-4-methylbenzene (10a). White solid; mp 62–65 °C; ¹H NMR (400 MHz, CDCl₃): 2.30 (s, 3H), 7.13 (m, 2H), 7.62 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): 20.9, 94.2, 126.7, 130.1, 132.3, 136.1, 139.1, 139.9. IR (KBr, cm⁻¹): 2916, 2134, 1633, 1474, 1042, 929, 811. C₈H₆INS (275.11): calcd. C, 34.92; H, 2.20; N, 5.09; S, 11.65. Found: C, 35.02; H, 2.24; N, 4.98; S, 11.59. MS (ESI): 275 (M⁺).

5-(Isothiocyanatomethyl)benzo[d][1,3]dioxole (14a). Oily liquid; ¹H NMR (400 MHz, CDCl₃): 4.59 (s, 2H), 5.98 (s, 2H), 6.74–6.80 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): 48.7, 101.5, 107.7, 108.6, 120.7, 128.0, 132.1, 147.8, 148.2. IR (KBr, cm⁻¹): 2895, 2087, 1503, 1445, 1369, 1322, 1251, 1101, 1028, 924. C₉H₇NO₂S (193.23): calcd. C, 55.95; H, 3.65; N, 7.25; S, 16.56. Found: C, 56.12; H, 3.71; N, 7.18; S, 16.50. MS (ESI): 194 (M + H⁺).

4-(2-Isothiocyanato-ethyl)-1,2-dimethoxy benzene (17a). Oily liquid; ¹H NMR (400 MHz, CDCl₃): 2.90 (t, 2H, $J = 6.6 \text{ Hz}$), 3.68 (t, 2H, $J = 6.6 \text{ Hz}$),

3.85 (s, 3H), 3.88 (s, 3H), 6.79 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): 36.0, 46.6, 55.85, 55.87, 111.3, 111.9, 120.8, 129.5, 130.3, 148.0, 148.9. IR (KBr, cm^{-1}): 3000, 2935, 2835, 2181, 2100, 1592, 1515, 1455, 1347, 1263, 1142, 1028, 909. $\text{C}_{11}\text{H}_{13}\text{NO}_2\text{S}$ (223.30) calcd.: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.08; H, 5.89; N, 6.22; S, 14.33.

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