A one-pot preparation of cyanamide from dithiocarbamate using molecular iodine†

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An efficient one-pot method for the synthesis of cyanamides from dithiocarbamate salts *via* a double desulfurization strategy using molecular iodine is disclosed. Dithiocarbamates, by the action of iodine yield isothiocyanates *in situ*, which on treatment with aqueous NH_3 give thioureas. The thioureas so generated undergo further oxidative desulfurization with I_2 giving corresponding cyanamides in good yields. Environmental benignity, cost effectiveness and high yields are the important attributes of this one pot procedure.

Introduction

Alkyl and aryl cyanamides are an important class of compounds which are vital intermediates for the synthesis of various biologically active molecules and can be converted efficiently into other functionalities by simple chemical reactions. Due to their unique structure and reactivity, cyanamides have attracted considerable attention in organic synthesis[1] as well as in the fields of inorganic and material sciences.[2] Cyanamides are key precursors to N-alkyl or N-aryl imides[3] and also serve as useful protecting groups in the synthesis of heterocycles containing secondary and tertiary amines.[4] They are important precursors in the synthesis of herbicides[5] and pharmaceutically active heterocycles such as tumor inhibitors,[6] and a vasodilator medication called minoxidil,[5] known for its ability to reduce hair loss and promote hair regrowth.

The wide applications of cyanamides have resulted in the development of several methods for their synthesis over the years. Commonest among these is the reaction of cyanogen chloride/bromide with amines or with imide salts.[7] However this method involves the use of potassium/sodium cyanide and bromine for the preparation of cyanogen halide (which is again highly toxic), making the protocol environmentally unacceptable.

Literature reports various other methods for preparation of cyanamide using different synthetic strategies such as cyanation of amines using CN^+ equivalents as synthons,[8–14] Tiemann rearrangement of amidoximes,[15] coupling reactions involving Pd isocyanides, allyl carbonates and trimethylsilyl azide,[16] and sodium bis(trimethylsilyl)amide as deoxygenating or desulfurizing agents.[17] Yet another method for the preparation of cyanamides involves the reaction of hypervalent iodine (V) species with *N,N′*-disubstituted glycylamide.[18] However, all the procedures reported so far seem to have severe environmental concern as they involve direct or indirect use of toxic and corrosive reagents, strong alkaline conditions, expensive reagents and catalysts, high reaction temperatures and tedious purification procedures.

We have been interested to an extent in the synthesis of isothiocyanates and cyanamides and in this context we recently developed a method involving hypervalent iodine reagent, diacetoxyiodobenzene (DIB) as an efficient thiophilic/desulfurizing agent for the preparation of these compounds from dithiocarbamate salts.[19] However, this method although efficient, is not economically viable when applied to large scale reactions. In yet another related work, we demonstrated that the hypervalency of iodine is not really essential, particularly for the transformation of dithiocarbamate to isothiocyanate and molecular iodine was found to be equally effective.[20] In continuation of these studies, and also while looking at reaction strategies from a Green chemistry perspective, we thought it would be worthwhile to investigate an alternative methodology for the synthesis of cyanamides, involving the use of alkyl or aryl dithiocarbamate using iodine as a double desulfurizing agent.

Results and discussion

Our present methodology is based on: (i) formation of isothiocyanate from alkyl/aryl dithicarbamate salt by desulfurization with iodine in the presence of triethylamine as the base in ethylacetate solvent, (ii) treating the *in situ* generated isothiocyanate with aqueous NH_3 to afford alkyl/aryl thioamides and (iii) further oxidative desulfurization of thioamides to cyanamide with iodine in the presence of triethylamine (Scheme 1). Using aqueous NH_3 as the base instead of triethylamine did not work as expected, due to the competing reactions between ammonia and molecular iodine forming nitrogen triiodide (NI_3), which of course is well documented in literature.[21] The mechanism which is proposed in the scheme has been authenticated by isolation and characterization of all the intermediates. Isolation of the precipitated elemental sulfur further supports the mechanism proposed.

Based on these findings, we thus report herein, a practical, environmentally benign, high yielding and one-pot preparation

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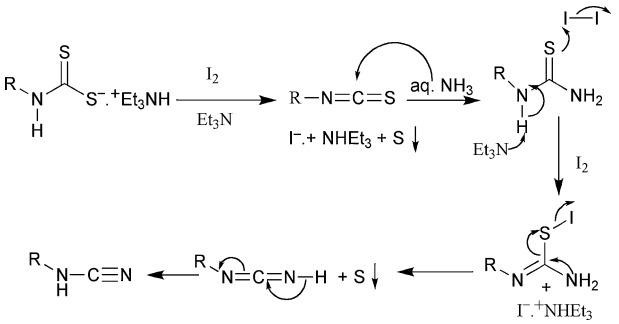
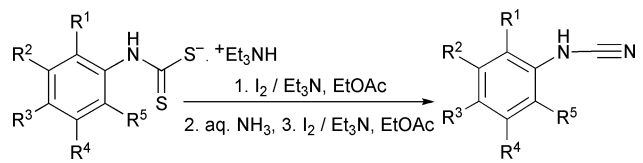


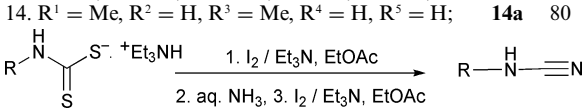
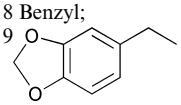
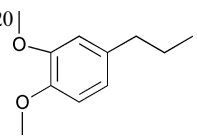
Scheme 1 Plausible mechanism for the formation of cyanamide.

of cyanamides from dithiacarbamate salts using cheap and non-toxic reagent molecular iodine (Scheme 1) in an innocuous solvent ethylacetate.

A variety of substituted aromatic dithiocarbamate salts[22] undergo facile transformation to give their corresponding cyanamides by this methodology (Table 1). This methodology is equally effective irrespective of the nature and positions (*o*-, *m*-, *p*-) of the substituents attached to the phenyl ring. Strongly activating (**2**, **7** and **10**), weakly deactivating (**3**, **4**, **5** and **9**), moderately deactivating (**8**) and strongly deactivating (**6**) systems all give products with equal ease. The versatility of the method has been demonstrated by the tolerance of a number of functional groups such as $-NO_2$ (**6**), –OMe (**2**, **7**), $-COCH_3$ (**8**) and –OH (**10**). Hindered and trisubstituted dithiocarbamate (**11–14**) also efficiently give their corresponding cyanamides (**11a–14a**) in excellent yields. As shown in Table 1, dithiocarbamates of napthylamine (**15**), aliphatic amines (**16** and **17**) and benzylic amines (**18** and **19**) give their corresponding cyanamides in good yields. This method has also been successful in the preparation of cyanamide (**20a**) of homoveratryl amine starting from its dithiocarbamate salt (**20**).

Table 1 Preparation of cyanamides from dithiocarbamates and iodine[a]



Substrate		Product[b] Yield (%)[c]
1. $R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 = H$, $R^5 = H$;	**1a**	80
2. $R^1 = OMe$, $R^2 = H$, $R^3 = H$, $R^4 = H$, $R^5 = H$;	**2a**	72
3. $R^1 = Br$, $R^2 = H$, $R^3 = H$, $R^4 = H$, $R^5 = H$;	**3a**	80
4. $R^1 = Cl$, $R^2 = H$, $R^3 = H$, $R^4 = H$, $R^5 = H$;	**4a**	70
5. $R^1 = F$, $R^2 = H$, $R^3 = H$, $R^4 = H$, $R^5 = H$;	**5a**	75
6. $R^1 = H$, $R^2 = NO_2$, $R^3 = H$, $R^4 = H$, $R^5 = H$;	**6a**	79
7. $R^1 = H$, $R^2 = H$, $R^3 = OMe$, $R^4 = H$, $R^5 = H$;	**7a**	78
8. $R^1 = H$, $R^2 = H$, $R^3 = COMe$, $R^4 = H$, $R^5 = H$;	**8a**	77
9. $R^1 = H$, $R^2 = H$, $R^3 = Cl$, $R^4 = H$, $R^5 = H$;	**9a**	65
10. $R^1 = H$, $R^2 = H$, $R^3 = OH$, $R^4 = H$, $R^5 = H$;	**10a**	75
11. $R^1 = Br$, $R^2 = H$, $R^3 = Me$, $R^4 = H$, $R^5 = H$;	**11a**	75
12. $R^1 = F$, $R^2 = H$, $R^3 = F$, $R^4 = H$, $R^5 = H$;	**12a**	81
13. $R^1 = I$, $R^2 = H$, $R^3 = Me$, $R^4 = H$, $R^5 = H$;	**13a**	73
14. $R^1 = Me$, $R^2 = H$, $R^3 = Me$, $R^4 = H$, $R^5 = H$;	**14a**	80
		
15 α-Naphthyl;	**15a**	80
16 Cyclohexyl;	**16a**	72
17 n-Butyl;	**17a**	60
18 Benzyl;	**18a**	82
19 	**19a**	72
20 	**20a**	60

[a] Reactions were monitored by TLC. [b] Confirmed by IR, ^1H NMR and ^{13}C NMR. [c] Isolated yield.

Conclusion

In conclusion, we have developed a general, economical and environmentally benign method for the preparation of cyanamides from their corresponding dithiocarbamic acid salts. Although literature enumerates a number of procedures for the preparation of cyanamides, the simplicity, environmental acceptability, and cost effectiveness of this one pot strategy makes it a practical alternative. Though at first glance the product yields of the reactions seem to be moderate or maybe just good, but when the fact that these are actually three step reactions done in a single-pot is brought to mind, the yields could infact be considered as very good if not excellent.

Experimental

All the reagents were commercial grade and purified according to 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 size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz). IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer. GC-MS were recorded using a capillary column (30 × 0.25 mm × 0.25 μM) in EI mode. Elemental analysis was performed with a Perkin Elmer 2400 elemental analyzer. Melting points were recorded on Buchi B-545 melting point apparatus and are uncorrected.

General procedure

To a stirred and ice cooled suspension of dithiocarbamate **1** (540 mg, 2 mmol) in ethylacetate (5 mL), was added triethylamine (415 μl, 3 mmol). To this was then added iodine (506 mg, 2 mmol) pinch wise over a period of 10–15 minutes to yield phenylisothiocyanate. During this period precipitation of elemental sulfur and triethylammonium iodide salt was observed. After complete addition of iodine, 25% aqueous NH_3 (2.5 mL) was added drop wise to the stirred reaction mixture to give 1-phenylthiourea. After stirring for 10 minutes at room temperature the excess of NH_3 was removed in a rotary

evaporator whereby the solvent ethylacetate was also simultaneously removed leaving behind the aqueous layer. To the crude reaction mixture was then further added ethylacetate (5 mL) and triethylamine (553 µl, 4 mmol). To the resultant solution, iodine (506 mg, 2 mmol) was added in small pinches, during which further precipitation of elemental sulfur was observed. The conversion of 1-phenylthiourea to phenylcyanamide (**1a**) was observed within 5 minutes of the complete addition of iodine. Completion of the reaction was confirmed by TLC. The precipitated sulfur was filtered, washed with ethylacetate (2 × 5 mL). The organic layer was washed with water (2 × 5 mL) and dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a short column of silica gel eluting it with hexane: ethylacetate (97:3) to give the pure product **1a** (188 mg, 80%). Oily liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.02–7.07 (m, 3H), 7.28–7.33 (m, 2H), 7.64 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 112.2, 115.5, 123.6, 129.8, 137.4; IR (KBr) 3175 (m), 2919 (w), 2227 (s), 1600 (s), 1501 (s), 1249 (m), 748 (s), 689 (m).

Spectral data

Spectral data for reported compounds:

1a–2a, **4a**, **6a**, **8a–10a**, **14a**, **16a–19a** are reported compounds.[19] The spectral data (IR, ^{1}H NMR, ^{13}C NMR, mass and CHNS of the new compounds are given below.

Selected spectral data

2-Bromo-phenyl cyanamide (3a). White solid; Mp: 94.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 6.36 (brs, 1H), 6.96–7.01 (m, 1H), 7.25–7.39 (m, 2H) 7.52–7.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 109.91, 109.95, 116.1, 124.9, 129.2, 133.0, 135.3; IR (KBr) 3150, 2237 (m), 1602 (m), 1504 (m), 1425 (w), 1286 (w), 1026 (w), 738 (m) cm^{-1}; elemental analysis for $C_7H_5BrN_2$ (197.03): calcd. C 42.67, H 2.55, N 14.21; found C 42.61, H 2.62, N 14.11.

2-Fluoro-phenyl cyanamide (5a). White solid; M.p: 95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 6.68 (brs, 1H, NH), 6.90–7.45 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 110.9, 115.7, 115.9, 116.8, 124.0, 124.1 125.09, 125.12, 125.6, 125.8, 150.1, 152.5. IR (KBr) 3339 (m), 3069 (m), 2233 (s), 1679 (m), 1621 (s), 1503 (s), 1455 (s), 1378 (m), 1266 (m), 1198 (m), 1109 (m), 1061 (m), 756 (s) cm^{-1}; elemental analysis for $C_7H_5FN_2$ (136.13): calcd. C 61.76, H 3.70, N 20.58; found C 61.80, H 3.73, N 23.53.

4-Methoxy-phenyl cyanamide (7a). White Solid; Mp: 86–89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.78 (s, 3H), 6.87 (d, 2H, J = 8.8 Hz), 6.95 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 55.8, 112.8, 115.2, 117.0, 130.6, 156.1; IR (KBr) 3180 (m), 2926 (m), 2218 (s), 1509 (s), 1295 (m), 1238 (s), 1105 (m), 1037 (m), 826 (m); elemental analysis for $C_8H_8N_2O$ (148.17): calcd. C 64.85, H 5.44, N 18.91; found C 64.91, H 5.40, N 18.93.

2-Bromo-4-methyl-phenyl cyanamide (11a). Brown solid; Mp: 91–93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.31 (s, 3H), 6.23 (brs, 1H), 7.14–7.19 (m, 2H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.5, 109.6, 110.4, 115.9, 129.8, 132.7, 133.2, 135.0; IR (KBr) 3211 (m), 2923 (w), 2226 (s), 1608 (w), 1509 (s), 1424 (m), 1287 (w), 1038 (w), 863 (w), 804 (m), 743 (w) cm^{-1}; elemental analysis for $C_8H_7BrN_2$ (211.06): calcd. C 45.52, H 3.34, N 13.27; found C 45.61, H 3.29, N 13.20.

2,4-Difluoro-phenyl cyanamide (12a). Gummy ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 6.06 (s, 1H), 6.88–6.96 (m, 2H), 7.20–7.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 104.0, 104.2, 104.3, 104.5, 111.27, 111.31, 111.50, 111.54, 111.69, 117.38, 117.41, 117.47, 111.50, 122.9, 123.0, 149.5, 149.7, 152.0, 152.1, 156.2, 156.3, 158.7, 158.8; IR (KBr) 3167 (m), 2927 (w), 2258 (s), 1611 (m), 1524 (s), 1433 (m), 1269 (m), 1215 (m), 1150 (m), 1125 (m), 1087 (m), 962 (m), 852 (m), 804 (m) cm^{-1}; elemental analysis for $C_7H_4F_2N_2$ (154.11): calcd. C 54.55, H 2.61, N 18.18; found C 54.61, H 2.58, N 18.20.

2-Iodo-4-methyl-phenyl cyanamide (13a). White solid; Mp: 144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.29 (s, 3H), 6.17 (brs, 1H), 7.17 (m, 2H), 7.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.4, 84.2, 110.7, 115.4, 130.9, 135.4, 139.6; IR (KBr) 3229 (s), 2919 (w), 2217 (s), 1603 (w), 1502 (s), 1420 (m), 1383 (m), 1283 (w), 1032 (w), 866 (w), 805 (m) cm^{-1}; elemental analysis for $C_8H_7IN_2$ (258.06): calcd. C 37.23, H 2.73, N 10.86; found C 37.28, H 2.68, N 10.80.

1-Naphthyl cyanamide (15a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 6.57 (s, 1H), 7.41 (m, 1H), 7.48 (m, 1H), 7.56 (m, 2H), 7.64 (d, 1H, J = 8 Hz), 7.75 (m, 1H), 7.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 110.9, 112.6, 120.5, 122.7, 123.1, 125.2, 125.5, 125.9, 127.8, 133.5, 133.7; IR (KBr) 3181 (m), 3052 (w), 2944 (w), 2234 (s), 1584 (w), 1530 (m), 1480 (s), 1403 (w), 1344 (w), 1258 (w), 782 (m), 758 (s) cm^{-1}; elemental analysis for $C_{11}H_8N_2$ (168.08): calcd. C 78.55, H 4.79, N 16.65; found C 78.49, H 4.78, N 16.58.

3,4-Dimethoxyphenylethylcyanamide (20a). Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.84 (t, 2H, J = 7.2 Hz), 3.28 (q, 2H, J = 7.2 Hz), 3.83 (s, 3H), 3.84 (s, 3H), 4.37 (brs, 1H), 6.72–6.82 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) δ 35.5, 47.5, 55.92, 55.95, 111.4, 111.9, 116.5, 120.9, 130.0, 147.8, 148.9. IR (KBr) 3274 (w), 2937 (w), 2219 (s), 1592 (w), 1517 (s), 1464 (m), 1262 (s), 1236 (m), 1156 (m), 1142 (m), 1026 (m), 913 (w) cm^{-1}; elemental analysis for $C_{11}H_{14}N_2O_2$ (206.24): calcd. C 64.06, H 6.84, N 13.58; found C 64.12, H 6.80, N 13.54.

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