Arylthioureas with bromine or its equivalents gives no 'Hugerschoff' reaction product[†]

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Received 5th March 2010, Accepted 27th May 2010 First published as an Advance Article on the web 16th June 2010 DOI: 10.1039/c003892j

The *in situ* generated aryl-alkyl unsymmetrical thiourea obtained by the reaction of an aryl isothiocyanate with an aliphatic secondary amine on treatment with bromine or its equivalent gave exclusively a product having a thioamido guanidino moiety and not the expected Hugerschoff product 2-aminobenzothiazole. A plausible reaction mechanism has been proposed for this unprecedented transformation and the scope has been extended to various substrates.

Introduction

The classical Hugerschoff reaction known since 1901 involves the reaction of a 1,3-diaryl thiourea and liquid bromine in chloroform medium to produce 2-aminobenzothiazole.¹ This reaction essentially involves the intramolecular aromatic electrophilic substitution reaction of an aryl ring to the thiocarbonyl group of a thiourea and the process is facilitated by thiophilic bromine. Subsequently, the same has been achieved with bromine equivalents such as benzyltrimethylammonium tribromide,² and [Bmim]Br₃³ in an ionic liquid in a controlled manner and is reported to give better yield with fewer side products. Irrespective of the reagents, Br₂ or its equivalents used, 1,3-diarylthiourea or aryl–alkylthioureas are reported to give 2-aminobenzothiazole as the major product. This is true even when one side of the thiourea is an arylamine and the other a secondary alkyl amine such as pyrrolidine or piperidine.^{2,3}

Results and discussion

In one of our ongoing projects, we treated phenyl isothiocyanate (1), (1 equiv.) and piperidine (a), (1 equiv.) in CH_2Cl_2 to which was added bromine equivalent, 1,2-dipyridiniumditribromideethane (DPTBE)⁴/[1,1'(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT)],⁵ a ditribromide reagent, and stirred for 1 h. The major product isolated (77%) was found to have a thioamido guanidino moiety (1a) and the minor product (~12%) was the expected 2-aminobenzothiazole (1a') as shown in Scheme 1. This observation was consistent even when the reaction was carried out with an isolated thiourea as shown in Scheme 1.

This result however, is in sharp contrast to the recent report by Jordan² and Le³ *et al.* where 2-aminobenzothiazole (1a') is reported to be the major product. The only difference between Jordan,² Le³ *et al.* and ours is the selection of the brominating



Scheme 1 Reaction products of the *in situ* generated thiourea with EDPBT.

 $Table 1 \ Reagent$ dependent reactivity of phenyl isothiocyanate and piperidine in CH_2Cl_2

| Entry | Brominating Reagent/time | Total isolated yield of $(1a) + (1a')$ | Ratio ^{<i>a</i>} of (1a): (1a') |
|-------|---|--|--|
| 1 | EDPBT/0.5 h | 89 | 77:12 |
| 2 | $Bu_4N^+Br_3^-/0.5h$ | 86 | 70:16 |
| 3 | $[Bmim^{b}]^{+}Br_{3}^{-}/1h$ | 78 | 48:30 |
| 4 | PhCH ₂ N ⁺ Me ₃ Br ₃ $^-/1$ h | 85 | 68:17 |
| 5 | $CH_3(CH_2)_{15}N^+Me_3Br_3^-/3h$ | 80 | 73:7 |
| 6 | Br ₂ /1 h | 75 | 40:35 |

^{*a*} Isolated yields. ^{*b*} Bmim = 1-butyl-3-methylimidazolium.

reagent. We have been working on various bromine equivalents such as tetrabutylammonium tribromide (TBATB),⁶ and EDPBT^{4,5,7} for last decade. All these reagents are after all bromineless brominating reagent with similar reactivity hence we have never encountered any major change in their reactivity/selectivity. Thus, there is no reason why the product obtained using different brominating reagents should be so much different. In order to ascertain this, the same reaction was performed in CH_2Cl_2 with different brominating reagents including bromine and the result is summarised in Table 1.

As can be seen from Table 1, irrespective of the brominating reagent used, the formation of the product containing a thioamido guanidino moiety (1a) is always the dominant over the expected 2aminobenzothiazole (1a'). The difference in distribution of two products with various brominating reagents listed in Table 1 could possibly be due to the intrinsic acidity caused by these reagents in the reaction medium. Acidity is dependent on the nature of the reagent *i.e.* counter cation present in a given solvent. It may be mentioned here that in a classical Hugerschoff reaction the substrates employed are 1,3-diarylthioureas, where the arylamines are primary and not secondary in nature. These kind of substrates invariably gives Hugerschoff product 2-aminobenzothiazole irrespective of the nature of brominating reagents used. However the difference is noticed only when one side of the thiourea is having a primary arylamine and the other side a secondary aliphatic amine. Thus, in the latter case irrespective of the brominating reagent (Table 1) used the

Indian Institute of Technology Guwahati, Guwahati 781 039, Assam, India. E-mail: patel@iitg.ernet.in; Fax: +91-361-2690762; Tel: +91-361-2582307 † Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra. CCDC reference numbers 754857–754861. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c003892j

| Entry | Solvent/time | Total isolated yield of (1a)+(1a') | Ratio "(1a):(1a') | |
|-------|--|------------------------------------|-------------------|--|
| 1 | CH ₂ Cl ₂ /0.5 h | 89 | 77:12 | |
| 2 | $CH_{3}CN/0.5 h$ | 82 | 68:14 | |
| 3 | Dioxane/1.5 h ^b | 75 | 60:15 | |
| 4 | THF/1.5 h ^b | 92 | 85:7 | |
| 5 | THF/1.5 h | 94 | $94:0^{\circ}$ | |
| 6 | MeOH/0.5 h | 80 | $80:0^{d}$ | |
| 7 | DMF/0.5 h | 78 | 78:0 | |
| 8 | AcOH/0.5 h | 77 | 55:22 | |
| | | | | |

^{*a*} Isolated yields. ^{*b*} Possibly due to lesser solubility of EDPBT reagent. ^{*c*} Reaction was performed with 0.25 eq. of EDPBT. ^{*d*} Some other minor side products were also obtained.

anti-Hugerschoff *i.e* product containing a thiomido guanidino moiety (**1a**) is the major product (Table 1). The results of Jordan,² Le³ *et al.* even under their reported condition could not be reproduced in our hand. We always obtained a thioamido guanidino moiety (**1a**) as the major product and 2-aminobenzothiazole (**1a**') as the minor product, where as they have reported the exclusive formation of 2-aminobenzothiazole under an identical condition.

Next, we wished to investigate the effects of various solvents on the distribution of products (1a) and (1a'). The above reaction was performed in various organic solvents listed in Table 2 using 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) in the ratio of 1:0.5 equiv. of the thiourea and EDPBT. Since EDPBT used here is 0.5 equivalents (being a ditribromide reagent the bromine content is 1 equivalent). From Table 2, it is evident that irrespective of the solvents used, the major product is having a thioamido guanidino moiety (1a). Better selectivity was obtained in THF compared to other solvents, possibly due to the controlled release of bromine from EDPBT due to its partial solubility (Table 2, entry 4). Even using of 0.25 equiv. of EDPBT resulted the exclusive formation of 1a (Table 2, entry 5).

A mechanism as shown in Scheme 2 can be proposed to account for the formation of the product (1a). This mechanism essentially involves the formation of a disulfide intermediate (Z) followed by the attack of one of the iminium nitrogens on to the adjacent iminium carbon with the concurrent expulsion of elemental sulfur to give the desired product (1a) as shown in Scheme 2.



Scheme 2 Proposed mechanism for the formation of (1a).

In order to ascertain this mechanism, a crossover experiment as shown in Scheme 3 was performed. The *in situ* generated thioureas from their corresponding isothiocyanates (2 and 8) and morpholine (b) on treatment with EDPBT gave three products, 2b, 2e and 8b, isolated in 8%, 78% and 11% yields respectively. In this reaction, two symmetrical disulfides (K) and (L) and an unsymmetrical disulfide (M) (Scheme 3) is expected to form in the medium. Products 2b and 8b can originate from their corresponding symmetrical disulfides (**K**) and (**L**) respectively. However, formation of the major product 2e can be explained if there is formation of a mixed disulfide (**M**) as shown in Scheme 3. In principle, the intramolecular attack of the two different imino nitrogens on to the adjacent imino carbons of the mixed disulfide (**M**) is expected to result in two isomeric products. Interestingly, the formation of only one of the isomeric products was clearly observed. The structure of the product (**2e**) has been unequivocally confirmed by X-ray crystallographic analysis as shown in Fig. 1.⁸



Fig. 1 ORTEP molecular diagram of 2e.⁸ H atoms are omitted for clarity.



Scheme 3 Crossover experiment and product distribution.

Previously, we have observed a good correlation between pK_a 's of the amines and the regioselective *N*-acylation of thioureas^{9a} and also during the formation of 2-imino-4-thiazolidinones.^{9b} Having the knowledge of pK_a 's of the amines^{7b,7e} and reactivity of the thioureas,⁹ one can account for the exclusive formation of the product (**2e**). Due to the higher pK_a of *p*-methyl aniline ($pK_a = 5.08$) compared to *o*-chloro aniline ($pK_a = 2.65$), the imine nitrogen of the former is expected to be more nucleophilic and hence preferentially attack in an intramolecular fashion as shown in Scheme 2 and 3 giving the major product (**2e**). Further, due to the lower pK_a of *o*-chloroaniline ($pK_a = 2.65$) its imine nitrogen preferentially gets protonated over the other imine of the intermediate (**M**) there by enhancing the electrophilicity of the imine carbon of *o*-chloroaniline as shown in Scheme 3.

The scope of this reaction has been demonstrated with various aliphatic secondary amines such as piperidine (**a**), morpholine (**b**), pyrrolidine (**c**) and di-*n*-butylamine (**d**) to give major products (**1a**), (**1b**), (**1c**), and (**1d**) respectively, all possessing the thioamido guanidino moiety as shown in Table 3. Structure of the product **1a** has been confirmed by crystal X-ray crystallography as shown

 Table 3
 Reaction of phenyl isothiocyanates with secondary amines and DPTBE/EDPBT^a

Isothiocyanate Sec.amine/time/h Product^b, yield (%)^c



^{*a*} Reactions were monitored by TLC. ^{*b*} Confirmed by IR, ¹H NMR and ¹³C NMR. ^{*c*} Isolated yield. ^{*d*} nd = not detected

in Fig. 2.¹⁰ In all these cases, the Hugerschoff product 2aminobenzothiazole was obtained as a minor products (**1a**' or **1c**') as shown in Table 3, or not observed at all.



Fig. 2 ORTEP molecular diagram of 1a.¹⁰ H atoms are omitted for clarity.

The success of this strategy was then applied to various other aryl isothiocyanates (Table 4). Substrates (2) and (3) containing weakly deactivating substituents (Cl and Br) in the ortho position gave 2b, 2c and 3b respectively, as the exclusive products. Aryl isothiocyanate having a strong electron withdrawing group (-NO₂) (4) in its *meta* position on reaction with piperidine (a), followed by treatment with EDPBT gave 4a as the only isolated product. Further, weakly deactivating substituents (Cl and Br) when present in the para-position of an isothiocyanates (5 and 6), when reacted with aliphatic secondary amines such as morpholine (b) and piperidine (a) followed by treatment with EDPBT yielded the thioamido guanidino moiety containing products 5b, 6a and 6b. The structure of the products 5b and 6a have been further confirmed by crystal Xray crystallography (see supporting informations). Isothiocyanate (7) containing strongly deactivating substituent (-CF₃) in its para position gave sole products 7b and 7c respectively, when reacted with a secondary amines morpholine (b) and pyrrolidine (c) under the identical condition. Even isothiocyanates (8 and 9) having moderately activating groups (Me and OMe) in its para position gave no significant amount of benzothiazoles 8b' and 9c' and the dominant product was still the anti-Hugerschoff product 8b and 9c respectively.

Table 4 Reaction of arylisothiocyanates with secondary amines and EDPBT^{α}



^{*a*} Reactions were monitored by TLC. ^{*b*} Confirmed by IR, ¹H NMR and ¹³C NMR spectroscopy. ^{*c*} Isolated yields. nd = not detected.

 Table 5
 Reaction of activated aryl isothiocyanates with secondary amine and EDPBT^a



^{*a*} Reactions were monitored by TLC. ^{*b*} Confirmed by IR, ¹H NMR and ¹³C NMR spectroscopy. ^{*c*} Isolated yields. ^{*d*} Complete conversion was observed with in 1 h.

Except isothiocyanates (8 and 9), all other aryl isothiocyanates listed in Table 4 are either moderately deactivated or strongly deactivated. Thus, they are expected to be less susceptible towards intramolecular electrophilic substitution to give Hugerschoff product 2-aminobenzothiazole and are more likely to yield the intermolecular nucleophilic substitution product i.e *anti*-Hugerschoff product. In order to ascertain this effect, we selected some activated aryl isothiocyanates (10) and (11) as shown in Table 5.

Interestingly, morpholine thiourea of isothiocyanate (10) when reacted with EDPBT gave two inseparable regioisomeric benzothiazoles 10b' and 10b"; in the ratio of 3:2. Surprisingly, when the secondary amine was changed to pyrrolidine (c), (10c') was the lone isolated product. 1-Isothiocyanato napthalene (11), an activated fused aromatic substrate, under went intramolecular electrophilic substitution reaction giving exclusively napthothiazoles **11b**' and **11c**' respectively, in good yield.

Conclusions

In conclusion, we have demonstrated that some of the activated and all the deactivated aryl thioureas under the Hugerschoff reaction condition (bromine or its equivalents) gave a product having a thioamido guanidino moiety (*anti*-Hugerschoff product) as the major product. The formation of *anti*-Hugerschoff reaction goes *via* a disulfide intermediate which has been supported by a cross-over experiment. Further, we have observed that the generally expected Hugerschoff product is the major product only when the aryl ring is sufficiently activated.

Experimental

General remarks

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Reaction progress was monitored by TLC using Merck silica gel 60 F₂₅₄ (0.25 mm) with detection by UV or iodine. Chromatography was performed using Merck silica gel (60-120) mesh size with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded on a Varian FT-400 MHz instrument using TMS as an internal standard. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, b= broad, br s = broad singlet, br m = broad multiplet, coupling constant J (Hz). Elemental analyses were carried out on a Perkin-Elmer 2400 automatic carbon, hydrogen, nitrogen and sulfur analyser. Melting points were recorded on Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer. Mass data were obtained with a WATERS MS system, Q-tof premier and data analyzed using Mass Lynx4.1.

Crystallographic Analysis

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite by using graphite-monochromated Mo-K α radiation ($\lambda = 0.71073$ Å) at 298 K. Cell parameters were retrieved using SMART¹¹ software and refined with SAINT¹¹ for all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentzian and polarization effects. Absorption corrections were applied with the SADABS program.¹² The structures were solved by direct methods implemented in the SHELX-97¹³ program and refined by full-matrix least-squares methods on F^2 . All non-hydrogen atom positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. The crystals were isolated in rectangular shape from ethyl acetate and hexane mixture at room temperature.

General experimental procedure

General procedure for the preparation of guanidine (1a) from phenylisothiocyanate and piperidine (a). To a solution of phenylisothiocyanate 1 (270 mg, 2 mmol.) in THF (2 mL) was added drop wise piperidine a (197 µL, 2 mmol), dissolved in THF (2 mL) at room temperature. Formation of thiourea was observed within 15 min as judged from TLC. To this was then added EDPBT (666 mg, 1 mmol.) pinch wise over a period of 10 min. The reaction was kept for stirring at room temperature and complete conversion to anti-Hugerschoff product was observed within 1 h as can be judged from TLC and from the disappearance of the orange colour of EDPBT. After completion of the reaction, solvent was evaporated and the reaction mixture was admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with a saturated solution of NaHCO₃ (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The pure product was isolated by recrystallisation using ethyl acetate and hexane (8:2). Alternatively, the products can be purified by passing through a silica gel column (saturated with 1% triethyl amine) and eluted with hexane: ethylacetate (8:2) to give 1a (345 mg, 85%).

N-Phenyl-*N*-((*E*)-(phenylimino)(piperidin-1-yl)methyl)piperidine-1-carbothioamide (1a)

mp: 186–188 °C; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 0.84–1.67 (m, 12H), 2.63–3.82 (m, 8H), 6.90 (t, J = 7.6 Hz, 2H), 7.02–7.12 (m, 3H), 7.16 (t, J = 8.4 Hz, 2H), 7.26–7.40 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 23.6, 24.5, 24.6, 24.9, 47.4, 51.4, 122.1, 122.3, 124.1, 128.4, 129.2, 143.7, 149.7, 150.0, 184.9; IR (KBr): 2936, 2854, 1632, 1588, 1481, 1454, 1416, 1295, 1261, 1240, 1207, 1028, 989, 903, 749 cm⁻¹; MS (ESI): 407.2222 (MH⁺).

General procedure for the cross-over experiment

To a solution of o-chloro phenyl isothiocyanate 2 (338 mg, 2 mmol.) and *p*-methyl phenyl isothiocyanate 8 (298 mg, 2 mmol) in THF (2 mL) was added drop wise morpholine b (175 µL, 4 mmol), dissolved in THF (2 mL) at room temperature. Formation of corresponding thioureas was observed within 15 min as judged from TLC. To this was then added EDPBT (1332 mg, 2 mmol.) pinch wise over a period of 10 min. The reaction was kept for stirring at room temperature and complete conversion to anti-Hugerschoff product was observed within 2 h as can be judged from TLC and from the disappearance of the orange colour of EDPBT. After completion of the reaction, solvent was evaporated and the reaction mixture was admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with a saturated solution of NaHCO₃ (15 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The products were purified through a column of silica gel (saturated with 1% triethyl amine) and eluted with (hexane:ethylacetate 8:2) to give 2b (38 mg, 8%), 2e (358 mg, 78%), and 8b (48 mg, 11%).

N-((*E*)-(2-Chlorophenylimino)(morpholino)methyl)-*N*-(2-chlorophenyl)morpholine-4-carbothioamide (2b). mp: 157 °C; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 2.50–4.60 (m, 16H), 6.39–7.16 (m, 5H), 7.22–7.68 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 47.1, 47.5, 50.9, 66.1, 122.8, 123.9, 126.5, 127.3, 128.0, 129.1, 131.0,

139.7, 145.7, 148.6, 187.2; IR (KBr): 2950, 2894, 2849, 1632, 1580, 1470, 1427, 1401, 1363, 1303, 1272, 1237, 1219, 1206, 1159, 1150, 1119, 1109, 1051, 1031, 999, 953, 876, 757, 750 cm⁻¹; Elemental analysis: $C_{22}H_{24}Cl_2N_4O_2S$ (479.42): calcd C, 55.12; H, 5.05; N, 11.69; S, 6.69. found: C, 55.18; H, 5.09; N, 11.82; S, 6.75.

N-((E)-(2-Chlorophenylimino)(morpholino)methyl)-N-p-tolyl-

morpholine-4-carbothioamide (2e). mp: 133–134 °C; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 2.24 (s, 3H), 2.64–3.90 (m, 16H), 6.61 (br s, 1H), 6.83 (t, J = 7.6 Hz, 1H), 7.07 (t, J = 7.6 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 20.9, 47.1, 50.4, 65.4, 66.3, 120.2, 122.8, 123.5, 125.5, 126.4, 127.1, 129.5, 130.3, 134.8, 140.5, 146.2, 150.7, 186.2; IR (KBr): 2963, 2910, 2851, 1631, 1583, 1475, 1436, 1418, 1360, 1291, 1279, 1235, 1156, 1114, 1076, 1021, 998, 941, 851, 813, 754 cm⁻¹; Elemental analysis: C₂₃H₂₇ClN₄O₂S (459.00): calcd C, 60.18; H, 5.93; N, 12.21; S, 6.99. found: C, 60.14; H, 5.98; N, 12.14; S 7.93.

N-((*E*)-(*p*-Tolylimino)(morpholino)methyl)-*N*-*p*-tolylmorpholine-4-carbothioamide (8b)

Gummy; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 2.25 (s, 3H), 2.33 (s, 3H), 2.74 – 3.75 (m, 16H), 6.80 (br s, 1H), 6.85 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 7.08–7.27 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 20.8, 20.9, 46.7, 50.6, 65.4, 66.2, 121.2, 121.9, 129.2, 130.2, 131.8, 134.4, 140.2, 146.7, 149.5, 185.2; IR (KBr): 2963, 2919, 2857, 1632, 1607, 1506, 1472, 1422, 1360, 1296, 1279, 1236, 1160, 1115, 1066, 1034, 1018, 999, 940, 911, 855, 829, 818, 732 cm⁻¹; Elemental analysis: C₂₄H₃₀N₄O₂S (438.59): calcd. C, 65.72; H, 6.89; N, 12.77; S, 7.31. found C, 65.68; H, 6.84; N, 12.81; S, 7.26.

Acknowledgements

B. K. P acknowledges the support of this research by the Department of Science and Technology (DST) (SR/S1/OC-79/2009), New Delhi, and the Council of Scientific and Industrial Research (CSIR) (01(2270)/08/EMR-II). RY and SM thank the CSIR for fellowships. Thanks are due to Central Instruments Facility (CIF) IIT Guwahati for Mass and NMR spectra, and DST-FIST for XRD facility.

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