HETEROCYCLES, Vol. 57, No. 10, 2002, pp. 1799 – 1806, Received, 27th May, 2002

N-ARYLATION BY ARYL ISOCYANATES AS A GENERAL REACTION: USEFUL ROUTE TO DISUBSTITUTED *S,N*-DIARYLISOTHIOUREAS

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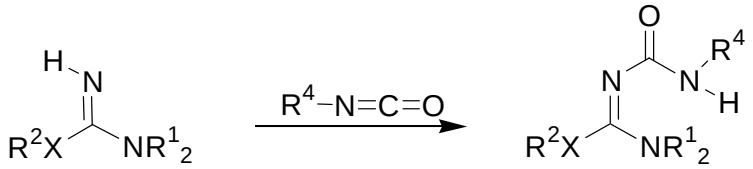
Abstract - *N*-Arylation of guanidines, isoureas and isothioureas by aryl isocyanates is demonstrated to have generality. Novel *N′*-arylations of *S*-arylisothioureas (**16**) with aryl isocyanates provide a new general route to biologically active *S,N′*-diarylisothioureas (**13**). Formation of (**13**) is explained as [2+2] cycloaddition of isoureas (**16**) to isocyanates followed by elimination of HNCO.

Reactions of C=NH containing guanidines (**1**, X = NR), isoureas (**1**, X = O) and isothioureas (**1**, X = S) with isocyanates R^4NCO to form the expected ureidoguanidines (**2**, X = NR), isobiurets (**2**, X = O) or isothiobiurets (**2**, X = S) by simple addition (Scheme 1; Table 1) are well recognized.[1]



1 **2**

Scheme 1

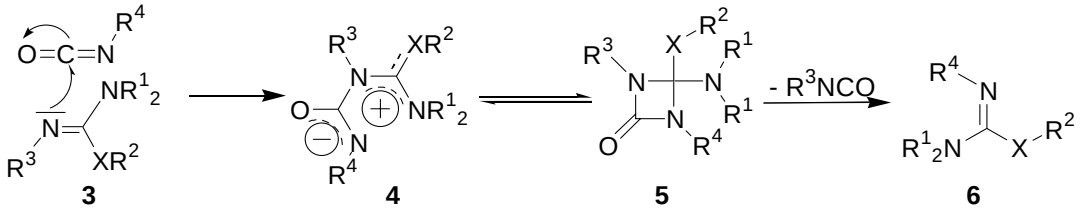
By contrast, scattered previous work has shown that compounds (**3**), analogous to (**1**), but carrying a substituent on the nitrogen, can react with isocyanates in a dramatically different manner leading to a replacement of this *N*-substitutent. Thus, penta- substituted guanidines (**3**) (X = NR, R^3 = Alk, Ar) react with tosyl (Table 2, Entries 1 2), benzoyl (Table 2, Entry 3) and thiobenzoyl isocyanates (Table 2, Entries 4, 5) with the loss of the original

Table 1. Addition reaction of isocyanates to imino compounds (**1**) (literature data).

Entry#	R^1, R^1	R^2	X	R^3	R^4	Conditions	**2**[ref]
1	Me, Me	Me	O	H	4-ClC_6H_4	a	62[1a]
2	Me, I-Pr	Me	O	H	4-ClC_6H_4	a	N/a[1a]
3	-$(CH_2)_5$-	Me	O	H	4-ClC_6H_4	a	N/a[1a]
4	H, H	Me	O	H	4-ClC_6H_4	a	84[1a]
5	Me, H	Me	O	H	4-ClC_6H_4	a	N/a [1a]
6	*i*-Pr, H	Me	O	H	4-ClC_6H_4	a	N/a[1a]
7	All, All	Ph	O	H	Ph	b	75[1b]
8	H, H	Me	O	H	H	c	75[1c]
9	H, H	Me	O	H	Me	a	96[1c]
10	H, H	Me	O	H	R*	d	94[1d]
11	Ph, Ph	Bn	S	H	Ph	e	75[1e]
12	Et, Et	Bn	S	H	Ph	e	70[1e]
13	*n*-Bu, *n*-Bu	Bn	S	H	Ph	e	71[1e]
14	Me, Ph	Bn	S	H	Ph	e	78[1e]
15	Me, Me	Me	MeN	H	Ph	a	65[1f]

Conditions: a) Et_2O,rt; b) petrol ether, rt; c) benzene, refl, 1 h, d) $CHCl_3$, rt, 1 h; e) PhH, refl, 4 h.

N′-substituent (R^3) as isocyanate to give tosyl-, benzoyl- and thiobenzoylguanidines (**6**).[3] The mechanism of this reaction has been explained[2a,3] as a [2+2] cycloaddition followed by the scission of intermediate (**5**) into compounds (**6**) and R^3NCO.



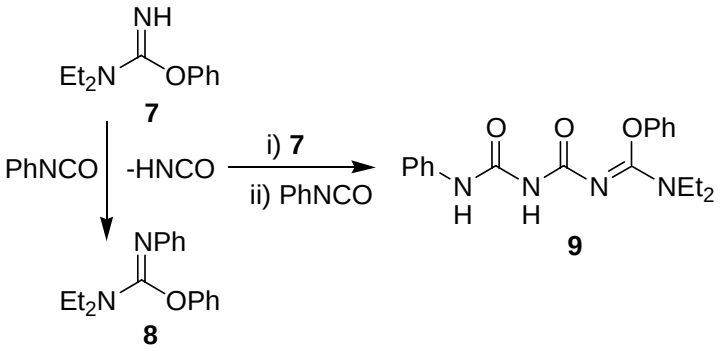
Scheme 2

Two examples (Table 2, Entries 6 and 7) were reported of the analogous formation of *S*-methylisothiourea. A single previously known formation of a *O*- phenylisourea (**8**) started from a *N′*-unsubstituted precursor (**7**) (Table 2, Entry 8):[3] reaction **7→8** was accompanied by the formation of triuret (**9**) as a result of sequential addition of the HNCO formed and of PhNCO to isourea (**7**) (Scheme 3)

Table 2. Reactions of imino compounds (**3**) with isocyanates *via* the formation of intermediates of [2+2] cycloaddition (literature data)

Entry#	R^1, R^1	R^2	X	R^3	R^4	Conditions	**6**[ref].
1	Me, Me	Me	MeN	n-Bu	4-$MeC_6H_4SO_2$	f	83.5[2a]
2	Me, Me	Me	MeN	Ph	4-$MeC_6H_4SO_2$	f	72[2a]
3	Me, Me	Me	MeN	Me	PhC=O	g	93[2b]
4	Me, Me	Me	MeN	Ph	PhC=S	h	76[2b]
5	Me, Me	Me	MeN	4-MeO-C_6H_4	PhC=S	h	52[2b]
6	Me, Me	Me	S	Me	4-$MeC_6H_4SO_2$	i	91[2c]
7	Me, Me	Me	S	Me	2,6-$MeC_6H_4SO_2$	i	90[2c]
8	Et, Et	Ph	O	H	Ph	a	40[3]

Conditions: a)Et_2O, rt; b) petrol ether, rt; c) benzene, refl, 1 h, d) $CHCl_3$, rt, 1 h; e) PhH, refl, 4 h; f) 1,2-ClC_6H_3, refl; g) Et_2O, -78 °C - rt; h) xylol : Et_2O = 1 : 3, rt, 1 h; i) Et_2O, -30 °C – rt; j) MePh, 100 °C, 18 h; k) MePh, 100 °C, 24 h; l) MePh, refl, 24 h; m) THF, rt, 24 h.



Scheme 3

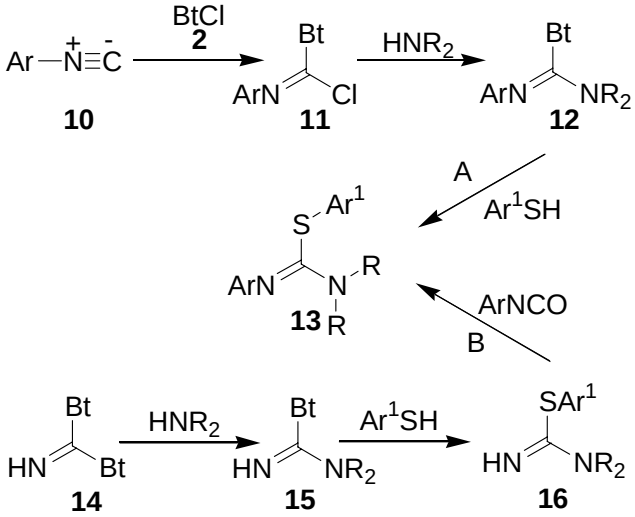
In some of this previous work (Table 2, Entries 1, 2), the intermediate adducts (**5**) ($R^3 \neq$ H) were completely characterized and required refluxing in 1,2-dichlorobenzene for conversion into compounds (**6**). However, most transformations of **5**→**6** proceed spontaneously.

The eight examples in Table 2 were reported in four different papers without cross referencing. The generality of reactions of this type was not previously recognized for various compounds of structure (**3**).

Isothioureas are useful as antivirals (in particular, against AIDS),[4] antihistamines,[5] insecticides,[6] acaricides,[7] and as herbicides.[8] The activity of isothioureas as selective blockers of nitric oxide synthase, and medicinal applications of this effect are widely reviewed,[9] and patented (e.g.[10]). Most of the isothioureas tested biologically are *S*-alkyl derivatives; this is probably explained by their easy preparation by *S*-alkylation of thioureas.

S-Arylisothioureas also show very interesting biological effects, such as antiviral[4] and antianginal[10f] activities. However, extensive biological screening of *S*-arylisothioureas has been restricted by synthetic limitations in their preparation. In contrast to the *S*-alkyl analogs, *S*-arylisothioureas can be prepared by direct arylation only from haloarenes activated *e.g.* by nitro groups.[11] *S*-(Dihydroxyaryl)isothioureas can be obtained by the addition of thioureas to quinones.[12] Similar reactions with 1,4-benzoquinone monooxime allow the synthesis of *S*-(5-amino-2-hydroxyphenyl)-substituted isothioureas.[13] These synthetic routes to *S*-arylisothioureas lack generality; the only known general procedure for the synthesis of *S*-arylisothioureas (particularly *S,N*-diarylisothioureas **13**) is the *S*-arylation of *N*-phenylthioureas with diazonium salts.[14] However, this reaction gives the desired derivatives in 9-50% yields after column chromatography,[14a] or in 26–60% yields as picrate salts.[14b]

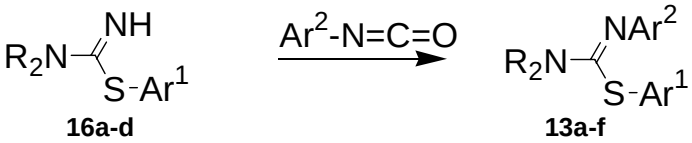
Recently, we disclosed examples of convenient preparations of *N′,S*-diarylisothioureas (**13**) starting from aryl isonitriles (**10**) followed by sequential reactions of intermediate chlorides (**11**) with amines, and intermediate benzotriazolecarboximidamides (**12**) with aromatic thiols (Scheme 4, route A).[15] However, the limited availability of isonitriles decreases the diversity possible at the *N′*-position.



Scheme 4

In the present work, we report versatile methodology for the *N′*-arylation of easily available *N,N*-disubstituted *S*-arylisothioureas of type (**16**) by their reaction with aryl isocyanates, a new general synthetic route to *S,N*-diaryl isothioureas (**13**) (Scheme 4, route B). Reaction of isothioureas (**16a-d**) with phenyl isocyanate in toluene at 100 ^{o}C for 18 h led to *N′*-phenyl derivative (**13a,d-f**) in 42-60% yield after column chromatography (Scheme 2). Similar reactions with 4-chlorophenyl isocyanate and 4-methoxyphenyl isocyanate gave the desired compounds (**13b**) and (**13c**) in 39% and 54% yields respectively. These results show the low sensitivity to the nature of a substituent in the aryl isocyanate; therefore, a variety of inexpensive, commercially available aryl

isocyanates can be applied for *N*′-arylation of isothioureas (**16**). Such *N*′-arylations of isothioureas by isocyanates were not previously reported (Scheme 5, Table 3, Entries 1-6).



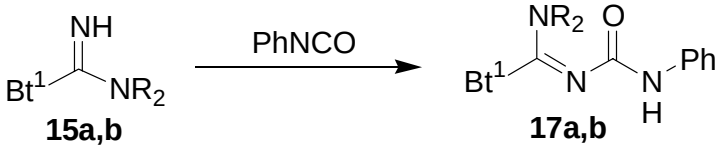
16a-d **13a-f**

Scheme 5

Table 3. Products from the reactions of isothioureas (**16**) and (benzotriazol-1-yl)carboximidamides (**15a,b**) with isocyanates.

Entry	Product	R_2	Ar^1	Ar^2	Yield,%
1	**13a**	$O(CH_2CH_2)_2$	4-ClC_6H_4	Ph	42
2	**13b**	$O(CH_2CH_2)_2$	4-ClC_6H_4	4-ClC_6H_4	39
3	**13c**	$O(CH_2CH_2)_2$	4-ClC_6H_4	4-$MeOC_6H_4$	54
4	**13d**	$(CH_2)_4$	3-$MeOC_6H_4$	Ph	56
5	**13e**	Et, Et	Ph	Ph	60
6	**13f**	*i*-Pr, *i*-Pr	4-$MeOC_6H_4$	Ph	45
7	**17a**	$O(CH_2CH_2)_2$	Bt^1	Ph	61
8	**17b**	Bn, Bn	Bt^1	Ph	85

These novel *N*′-arylations of isothioureas (**16**) to diaryl derivatives (**13**) (Scheme 4) depends on the electron-withdrawing properties of the ArS group. This type of reaction is not usual for less activated imino derivatives such as *S*-alkylisothioureas, or the benzotriazole derivatives (**15a,b**): these compounds reacted with phenyl isocyanate to give exclusively products of normal addition (**17a,b**) (Scheme 6) (Table 3, Entries 7,8).



15a,b **17a,b**

R,R = morpholino (**a**); Bn, Bn (**b**)

Scheme 6

In summary, we have uncovered, rationalized, and placed within its literature context a synthetically useful *N*′-arylation of *S*-arylisothioureas which should allow facile first time access to a wide variety of *S,N*′-diarylisothioureas.

EXPERIMENTAL

General comments: ^{1}H, ^{13}C NMR spectra were recorded on a 300 MHz NMR spectrometer (300 and 75 MHz respectively) using $CDCl_3$ as a solvent. Tetrahydrofuran (THF) was distilled under nitrogen immediately before use from sodium/benzophenone. Compounds (**15a,b**) and (**16a-d**) were prepared according to our previously described protocols.[16,17] All other reagents and solvents were obtained from commercial sources and were used without purification.

General procedure for the preparation of compounds (13a-c).

To a vigorously stirred solution of isothiourea (**16a-d**) (1 g, 3.9 mmol) in 60 mL of dry toluene, an appropriate isocyanate (3.9 mmol) was added at rt and the reaction mixture was heated at 100–110 ^{o}C for 18-24 h. Residue obtained after removal of toluene on rotary evaporator was purified by column chromatography on silica gel using 1:1 ethyl acetate/hexanes mixture as eluent. For the microanalytical purposes samples of compounds **13a-c,f** were additionally recrystallized from DCM.

Compound (13a). 4-Chlorophenyl-*N*-phenyl-4-morpholine-carbimidothioate. Colorless prisms, 42%, mp 77-79 °C. ^{1}H NMR δ 3.59 (br s, 8H), 6.71 (d, J = 7.7 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 7.08 - 7.19 (m, 6H); ^{13}C NMR δ 48.5, 66.4, 121.7, 122.7, 128.4, 129.0, 131.2, 132.4, 133.3, 149.6, 153.0. Anal. Calcd for $C_{17}H_{17}N_2OClS$: C, 61.35; H, 5.15; N, 8.42. Found: C, 61.39; H, 5.35; N, 8.41.

Compound (13b). 4-Chlorophenyl-*N*-(4-chlorophenyl)-4-morpholinecarbimidothioate. Colorless prisms, 39%, mp 85-86 °C. ^{1}H NMR δ 3.53-3.60 (m, 8H), 6.60 (d, J = 8.5 Hz, 2H), 7.02-7.15 (m, 6H); ^{13}C NMR δ 48.1, 66.1, 122.8, 127.5, 128.1, 128.8, 130.5, 132.2, 133.1, 148.0, 153.2. Anal. Calcd for $C_{17}H_{16}N_2OCl_2S$: C, 55.59; H, 4.39; N, 7.63. Found: C, 55.38; H, 4.47; N, 7.55.

Compound (13c). 4-Chlorophenyl-*N*-(4-methoxyphenyl)-4-morpholinecarbimidothioate. Colorless prisms, 54%, mp 76-78 °C. ^{1}H NMR δ 3.57 (br s, 8H), 3.75 (s, 3H), 6.65 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 48.4, 55.4, 66.4, 113.7, 122.5, 129.0, 131.4, 132.3, 133.2, 143.0, 153.3, 155.5. Anal. Calcd for $C_{18}H_{19}N_2O_2ClS$: C, 59.58; H, 5.28; N, 7.72. Found: C, 59.65; H, 5.46; N, 7.69.

Compound (13d). 3-Methoxyphenyl-*N*-phenyl-1-pyrrolidinecarbimidothioate. Colorless oil, 56%. ^{1}H NMR δ 1.87 (m, 4H), 3.55 (m, 4H), 3.71 (s, 3H), 6.62-6.70 (m, 2H), 6.72-6.82 (m, 3H), 6.91 (t, J=7.4Hz, 1H), 7.06-7.17 (m, 3H); ^{13}C NMR δ 25.2, 49.0, 55.1, 112.3, 115.1, 122.0, 122.1, 122.5, 128.2, 129.6, 134.4, 148.3, 150.5, 159.7. Anal. Calcd for $C_{18}H_{20}N_2OS$: C, 69.20; H, 6.45; N, 8.97. Found: C, 69.22; H, 6.76; N, 9.36.

Compound (13e). 1-[(Diethylamino)(phenylimino)methyl]sulfanylbenzene. Colorless oil, 60%. ^{1}H NMR δ 1.14 (t, J=7.0Hz, 6H), 3.56 (q, J=7.0Hz, 4H), 6.66 (d, J=7.6Hz, 2H), 6.86 (t, J=7.3Hz, 1H), 7.04-7.16 (m, 7H);

^{13}C NMR δ 13.4, 44.1, 121.6, 122.1, 126.4, 128.1, 128.6, 130.4, 133.5, 150.6, 150.8. Anal. Calcd for $C_{17}H_{20}N_2S$: C, 71.79; H, 7.09; N, 9.85. Found: C, 72.11; H, 7.48; N, 10.15.

Compound (13f). 1-{[(Diisopropylamino)(phenylimino)methyl]sulfanyl}-4-methoxybenzene. Colorless prisms, 45%, mp 73-75^{o}C. ^{1}H NMR δ 1.26 (d, *J*=6.6 Hz, 12H), 3.74 (s, 3H), 4.13-4.24 (m, 2H), 6.61-6.76 (m, 4H), 6.81 (t, *J*=7.2 Hz, 1H), 7.00-7.20 (m, 4H); ^{13}C NMR δ 21.1, 49.4, 55.3, 114.3, 121.1, 121.8, 124.1, 128.1, 133.4, 150.2, 150.6, 158.8. Anal. Calcd for $C_{20}H_{26}N_2OS$: C, 70.14; H, 7.65; N, 8.18. Found: C, 70.38; H, 7.94; N, 8.03.

General procedure for the preparation of compounds (17a,b).

Benzotriazole-1-carboximidamide (**15a,b**) (3.9 mmol) was dissolved in dry THF (40 mL) and phenyl isocyanate (465 mg, 3.9 mmol) was added under vigorous stirring. The resulting solution was allowed to react for 24 h at rt. Residue obtained after removal of toluene on rotary evaporator was purified by column chromatography on silica gel using 1:1 ethyl acetate/hexanes mixture as the eluent. For the microanalytical purposes samples of compounds (**17a,b**) were additionally recrystallized from acetone.

Compound (17a). *N*-Benzotriazol-1-yl(morpholino)methylidene-*N′*-phenylurea. Colorless prisms, 61%, mp 158-160 °C. ^{1}H NMR δ 3.54 (br s, 4H), 3.84-3.87 (m, 4H), 7.00 (t, *J* = 7.0 Hz, 1H), 7.19-7.32 (m, 4H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), signal of NH group does not appear; ^{13}C NMR δ 47.7, 66.3, 110.6, 118.9, 120.6, 123.4, 125.1, 128.8, 129.5, 132.7, 138.4, 145.4, 147.3, 157.4. Anal. Calcd for $C_{18}H_{18}N_6O_2$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.84; H, 5.44; N, 23.44.

Compound (17b). *N*-Benzotriazol-1-yl(dibenzylamino)methylidene-*N′*-phenylurea. Colorless prisms (85%), mp 215-217 °C. ^{1}H NMR δ 4.57 (s, 4H), 6.98 (t, *J* = 6.5 Hz, 1H), 7.17-7.41 (m, 15H), 7.44-7.55 (m, 2H), 8.08 (d, *J* = 8.4 Hz, 1H), signal of NH group does not appear; ^{13}C NMR δ 52.1, 110.2, 118.9, 120.5, 123.3, 124.8, 128.0, 128.1, 128.8, 128.9, 129.3, 133.0, 135.2, 138.5, 145.3, 148.6, 157.0. Anal. Calcd for $C_{28}H_{24}N_6O$: C, 73.02; H, 5.25; N, 18.25. Found: C, 72.88; H, 5.48; N, 18.02.

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