

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

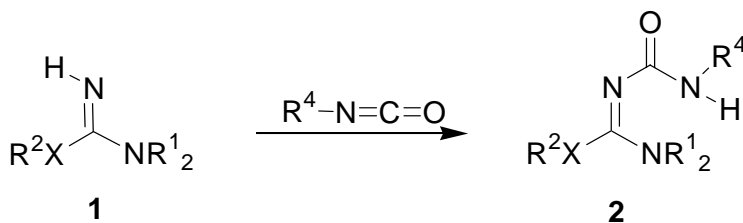
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Abstract - *N*-Arylation of guanidines, isoureas and isothiureas by aryl isocyanates is demonstrated to have generality. Novel *N'*-arylations of *S*-arylisothiureas (**16**) with aryl isocyanates provide a new general route to biologically active *S,N'*-diarylisothiureas (**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 isothiureas (**1**, X = S) with isocyanates R⁴NCO 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



Scheme 1

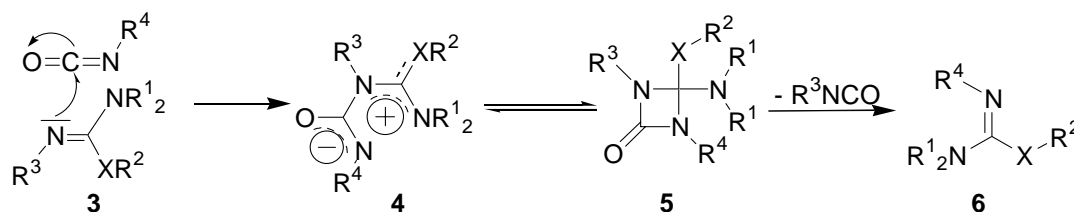
By contrast, scattered previous work has shown that compounds (**3**), analogous to (**1**), but carrying a substituent on the nitrogen, can react with isocyanates in a dramatically different manner leading to a replacement of this *N*-substituent. Thus, penta- substituted guanidines (**3**) (X = NR, R³ = 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 ₆ H ₄	a	62 ^{1a}
2	Me, <i>i</i> -Pr	Me	O	H	4-ClC ₆ H ₄	a	N/a ^{1a}
3	-(CH ₂) ₅ -	Me	O	H	4-ClC ₆ H ₄	a	N/a ^{1a}
4	H, H	Me	O	H	4-ClC ₆ H ₄	a	84 ^{1a}
5	Me, H	Me	O	H	4-ClC ₆ H ₄	a	N/a ^{1a}
6	<i>i</i> -Pr, H	Me	O	H	4-ClC ₆ H 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	<i>n</i> -Bu, <i>n</i> -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) Et₂O, rt; b) petrol ether, rt; c) benzene, refl, 1 h; d) CHCl₃, rt, 1 h; e) PhH, refl, 4 h.

N'-substituent (R³) 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 R³NCO.

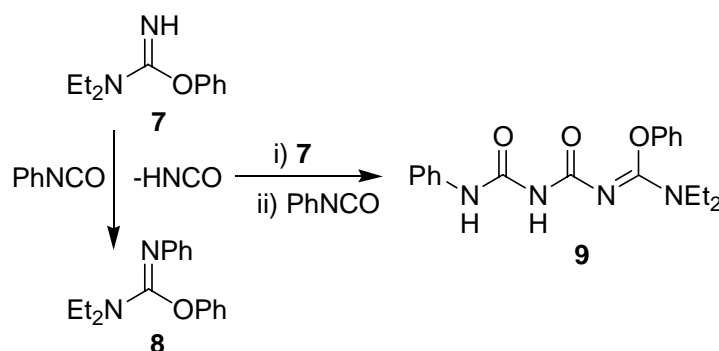
**Scheme 2**

Two examples (Table 2, Entries 6 and 7) were reported of the analogous formation of *S*-methylisothiurea. 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 ₆ H ₄ SO ₂	f	83.5 ^{2a}
2	Me, Me	Me	MeN	Ph	4-MeC ₆ H ₄ SO 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 ₆ H ₄	PhC=S	h	52 ^{2b}
6	Me, Me	Me	S	Me	4-MeC ₆ H ₄ SO ₂	i	91 ^{2c}
7	Me, Me	Me	S	Me	2,6-MeC ₆ H ₄ SO ₂	i	90 ^{2c}
8	Et, Et	Ph	O	H	Ph	a	40 ³

Conditions: a) Et₂O, rt; b) petrol ether, rt; c) benzene, refl, 1 h; d) CHCl₃, rt, 1 h; e) PhH, refl, 4 h; f) 1,2-ClC₆H₃, refl; g) Et₂O, -78 °C - rt; h) xylol : Et₂O = 1 : 3, rt, 1 h; i) Et₂O, -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

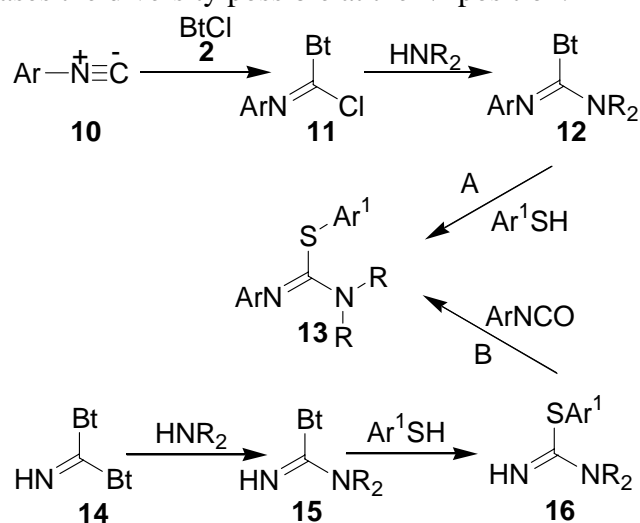
In some of this previous work (Table 2, Entries 1, 2), the intermediate adducts (**5**) ($R^3 \neq H$) were completely characterized and required refluxing in 1,2-dichlorobenzene for conversion into compounds (**6**). However, most transformations of **5**→**6** proceed spontaneously.

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-Arylisothiureas also show very interesting biological effects, such as antiviral⁴ and antianginal^{10f} activities. However, extensive biological screening of *S*-arylisothiureas has been restricted by synthetic limitations in their preparation. In contrast to the *S*-alkyl analogs, *S*-arylisothiureas can be prepared by direct arylation only from haloarenes activated *e.g.* by nitro groups.¹¹ *S*-(Dihydroxyaryl)isothiureas 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 isothiureas.¹³ These synthetic routes to *S*-arylisothiureas lack generality; the only known general procedure for the synthesis of *S*-arylisothiureas (particularly *S,N*-diarylisothiureas **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}

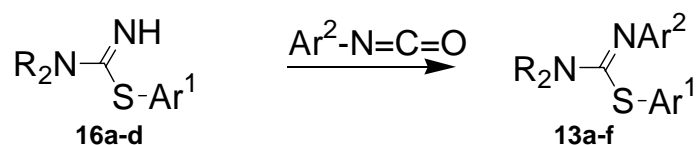
Recently, we disclosed examples of convenient preparations of *N',S*-diarylisothiureas (**13**) starting from aryl isonitriles (**10**) followed by sequential reactions of intermediate chlorides (**11**) with amines, and intermediate benzotriazolecarboximidamides (**12**) with aromatic thiols (Scheme 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*-arylisothiureas of type (**16**) by their reaction with aryl isocyanates, a new general synthetic route to *S,N*-diaryl isothiureas (**13**) (Scheme 4, route B). Reaction of isothiureas (**16a-d**) with phenyl isocyanate in toluene at 100 °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 isothiureas (**16**). Such *N'*-arylations of isothiureas by isocyanates were not previously reported (Scheme 5, Table 3, Entries 1-6).

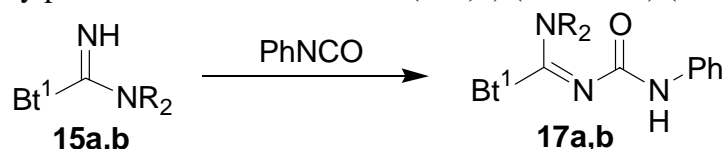


Scheme 5

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

Entry	Product	R ₂	Ar ¹	Ar ²	Yield,%
1	13a	O(CH ₂ CH ₂) ₂	4-ClC ₆ H ₄	Ph	42
2	13b	O(CH ₂ CH ₂) ₂	4-ClC ₆ H ₄	4-ClC ₆ H ₄	39
3	13c	O(CH ₂ CH ₂) ₂	4-ClC ₆ H ₄	4-MeOC ₆ H ₄	54
4	13d	(CH ₂) ₄	3-MeOC ₆ H ₄	Ph	56
5	13e	Et, Et	Ph	Ph	60
6	13f	<i>i</i> -Pr, <i>i</i> -Pr	4-MeOC ₆ H ₄	Ph	45
7	17a	O(CH ₂ CH ₂) ₂	Bt ¹	Ph	61
8	17b	Bn, Bn	Bt ¹	Ph	85

These novel *N'*-arylations of isothiureas (**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*-alkylisothiureas, 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).



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*-arylisothiureas which should allow facile first time access to a wide variety of *S,N'*-diarylisothiureas.

EXPERIMENTAL

General comments: ^1H , ^{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 °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. ^1H 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 $\text{C}_{17}\text{H}_{17}\text{N}_2\text{OClS}$: 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. ^1H 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 $\text{C}_{17}\text{H}_{16}\text{N}_2\text{OCl}_2\text{S}$: 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. ^1H 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 $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2\text{ClS}$: 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%. ^1H 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, $J=7.4\text{Hz}$, 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 $\text{C}_{18}\text{H}_{20}\text{N}_2\text{OS}$: 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%. ^1H NMR δ 1.14 (t, $J=7.0\text{Hz}$, 6H), 3.56 (q, $J=7.0\text{Hz}$, 4H), 6.66 (d, $J=7.6\text{Hz}$, 2H), 6.86 (t, $J=7.3\text{Hz}$, 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 $\text{C}_{17}\text{H}_{20}\text{N}_2\text{S}$: 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°C. ^1H 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 $\text{C}_{20}\text{H}_{26}\text{N}_2\text{OS}$: 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. ^1H 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 $\text{C}_{18}\text{H}_{18}\text{N}_6\text{O}_2$: 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. ^1H 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 $\text{C}_{28}\text{H}_{24}\text{N}_6\text{O}$: C, 73.02; H, 5.25; N, 18.25. Found: C, 72.88; H, 5.48; N, 18.02.

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