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Metathesis of Aryl Isothiocyanates: A Novel Method for the Synthesis of Sterically Hindered Aryl Isothiocyanates

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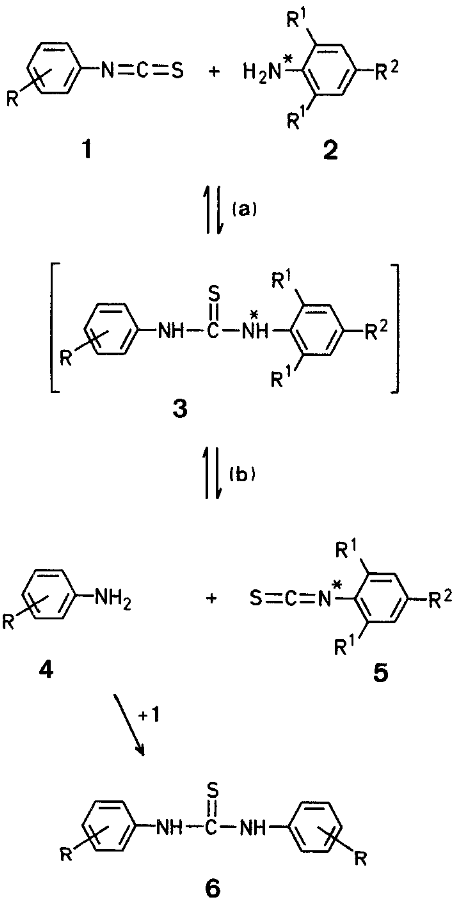
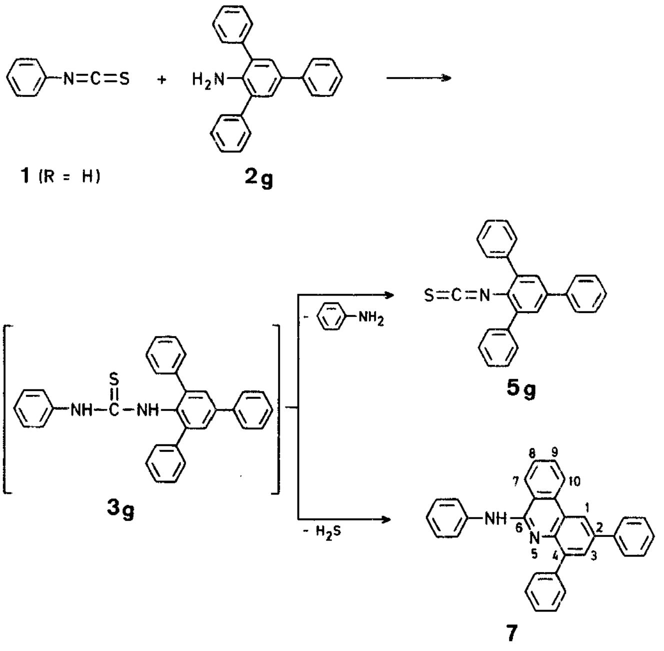
Most of the methods[1] reported for the synthesis of aryl isothiocyanates seem to be inconvenient and involve the use of carbon disulfide[2], carbon disulfide + triethylamine[3], decomposition of ammonium dithiocarbamates[4,5], or even the use of thiophosgene[6,7]. On the other hand, *N*-monoarylthioureas decompose to aryl isothiocyanates and ammonia when heated in a high-boiling solvent[8,9] whereas *N*,*N*'-diarylthioureas need the presence of acids to undergo cleavage to aryl isothiocyanates and anilines[10,11,12].

A more detailed inspection of the latter two reactions lead us to a new strategy for the synthesis of aryl isothiocyanates, the underlying concept being the assumption of a general reversibility of the well known[3] formation of *N*,*N*-diarylthioureas (**3**) from aryl isothiocyanates **1** and anilines **2** [equation (**a**), Scheme]. In the case of an unsymmetric thiourea **3**, this implies a second equilibrium (**b**) giving rise to aryl isothiocyanate **5** and aniline **4**. As a consequence, compounds **1** and **2** could finally form **4** and **5** via **3** (metathesis). Although the positions of the coupled equilibria (**a**) and (**b**) will depend on the nature of the substitutents R, R^1, and R^2, the reaction should proceed to **4** and **5** by the use of an excess of the isothiocyanate **1** which would directly act in terms of the mass law and also trap the produced aniline **4** to form a comparatively stable diarylthiourea **6**.



We now report that heating of sterically hindered anilines (**2**) with an excess of phenyl isothiocyanate (**1**; R = H) without solvent produces the sterically hindered aryl isothiocyanates **5a–h** in 68–97% yields (Table 1). Anilines of the type **2** seem to be most suitable for the metathesis reaction **1** + **2** → **4** + **5** since, according to space models, steric hindrance around the nitrogen atom N* in **5** is less than in either **2** or **3**.

Only the reaction with 2,4,6-triphenylaniline (**2g**) gave low yields of the desired isothiocyanate (**5g**) due to the formation of a second main product. According to microanalysis, M.S., and ^{1}H-N.M.R., we propose the structure of 6-anilino-2,4-diphenylphenanthridine (**7**) for this compound, which is in agreement with earlier investigations on *N*-aryl-*N*'-(biphenyl-2-yl)-thioureas[13].



All products were identified by microanalyses, mass spectra, I.R. spectrometry (the characteristic absorption of the N=C=S group appeared around ν = 2100 cm^{-1}), and ^{1}H-N.M.R. spectrometry. The ^{13}C-N.M.R. data, which are also in agreement with the isothiocyanate structure, will be reported elsewhere.

The unsymmetric thioureas **3** are presumably formed as the primary reaction products. Due to steric hindrance, they decompose in the presence of an excess of **1** (R = H) to the sterically hindered aryl isothiocyanates **5** and diphenylthiourea **6** (R = H). In agreement with this assumption, we

Table 1. Substituted Aryl Isothiocyanates (**5**) prepared from Anilines[a] (**2**) and Phenyl Isothiocyanate (**1**, R = H)

5	R^1	R^2	Method[a]	Reflux Time [h]	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[b] or Lit. Data [°C]	M.S. (70 eV)[c] *m/e* (rel. intensity)
a	CH_3	CH_3	A	2	90[d]	m.p. 61–62°	m.p. 64°[2]	177 (100), M^+; 162 (29); 144 (35); 119 (16)
			B	2	80[e]			
			C	2	90[e]			
b	i-C_3H_7	H	A	6	97[d]	b.p. 145°/14	b.p. 143–146°/14[3]	219 (100), M^+; 218 (34); 204 (75); 186 (27); 170 (33); 162 (45); 128 (25)
			B	6	80[e]			
			C	6	97[e]			
c	i-C_3H_7	i-C_3H_7	A	6	84[d]	oil[f]	$C_{16}H_{23}NS$ (261.4)	261 (74), M^+; 246 (100); 228 (8); 212 (8); 204 (23); 170 (11)
d	t-C_4H_9	t-C_4H_9	A	6	86[d]	m.p. 150–151° (methanol)	$C_{19}H_{29}NS$ (303.5)	303 (51), M^+; 288 (100); 232 (21); 57 (47)
e	t-C_4H_9	C_6H_5	A	6	93[d]	m.p. 163–164° (methanol)	$C_{21}H_{25}NS$ (323.5)	323 (100), M^+; 308 (38); 252 (45); 57 (25)
f	t-C_4H_9	OCH_3	A	3	68[d]	m.p. 50° (ether)	$C_{16}H_{23}NOS$ (277.4)	277 (100), M^+; 262 (38); 206 (65); 57 (23)
g	C_6H_5	C_6H_5	A	6	35[d,g]	m.p. 122–123° (methanol)	$C_{25}H_{17}NS$ (363.5)	363 (100), M^+; 330 (28)
h	J	J	A	4	92[d]	m.p. 160–161° (CH_2Cl_2/methanol)	$C_7H_2J_3NS$[h] (512.9)	513 (100), M^+; 259 (27)

[a] The anilines were commercial or obtained according to routine procedures: **2d**[14], **2e**[15], **2f**[16], **2g**[17].

[b] The microanalyses were in good agreement with the calculated values: N ±0.25; S ±0.33.

[c] $M^+ + 1$ and $M^+ + 2$ peaks (^{34}S) are also observed.

[d] Yield with respect to the corresponding aniline **2**.

[e] Yield with respect to the isolated thiourea **3**.

[f] Purified by column chromatography.

[g] The second main product formed is compound **7** (38%); see procedure.

[h] calc. J 74.23 N 2.73 S 6.25
found 73.77 2.68 6.61

Table 2. I.R.- and ^1H-N.M.R.-Spectral Data of Compounds **5**

5	I.R. (KBr) $\nu_{N=C=S}$ [a][cm^{-1}]	^1H-N.M.R. (solvent/TMS_{int}) δ [ppm]
a	2120, 2200[b]	($CDCl_3$): 2.27 (s, 3H, CH_3); 2.33 (s, 6H, $2CH_3$); 6.84 (s, $2H_{arom}$)
b	2090, 2140[b]	(CCl_4): 1.26 [d, J = 7 Hz, 12H, $2CH(C\underline{H}_3)_2$]; 3.23 [sp, J = 7 Hz, 2H, $2C\underline{H}(CH_3)_2$]; 6.8–7.3 (m, $3H_{arom}$)
c	2100	($CDCl_3$): 1.18 [d, J = 7 Hz, 6H, $CH(C\underline{H}_3)_2$]; 1.22 [d, J = 7 Hz, 12H, $2CH(C\underline{H}_3)_2$]; ~2.5–3.6 [m, 3H, $3C\underline{H}(CH_3)_2$]; 6.94 (s, $2H_{arom}$)
d	2150, 2180[b]	($CDCl_3$): 1.30 [s, 9H, $C(CH_3)_3$]; 1.44 [s, 18H, $2C(CH_3)_3$]; 7.31 (s, $2H_{arom}$)
e	2140, 2170[b]	(CCl_4): 1.49 [s, 18H, $2C(CH_3)_3$]; 7.2–7.6 (m, $7H_{arom}$)
f	2150, 2180[b], 2110[b]	(CCl_4): 1.45 [s, 18H, $2C(CH_3)_3$]; 3.71 (s, 3H, OCH_3); 6.69 (s, $2H_{arom}$)
g	2110, 2180[b]	(CCl_4): 7.2–7.6 (m, H_{arom})
h	2020, 2100[b], 1960[b]	($CDCl_3$): 8.07 (s, H_{arom})

[a] The absorption is strong and broad.

[b] Shoulder.

could isolate **3** in the case of medium hindrance, as for **a** ($R^1 = R^2 = CH_3$) and **b** (R^1 = i-C_3H_7, R^2 = H). Further heating of **3a, b** alone or with phenyl isothiocyanate finally produced the isothiocyanates **5a, b** and aniline or diphenylthiourea respectively.

The metathesis reaction of aryl isothiocyanates with anilines described here is a convenient, inexpensive and effective method for the synthesis of sterically hindered aryl isothiocyanates.

Substituted Aryl Isothiocyanates (5); General Procedures:

Method A: The aniline **2** (10 mmol) and phenyl isothiocyanate (**1**, R = H; 2.97 g, 22 mmol) are heated under reflux for 2–6 h (Table 1) in an oil bath (190 °C) whereupon a white flaky crystalline sublimate of diphenylthiourea (**6**, R = H) appears in the condenser. The mixture is cooled and quenched with petroleum ether (30 ml) to precipitate **6**. The filtrate is evaporated to dryness and the oily residue is crystallized from methanol (**5d, e**), or purified by vacuum distillation (**5a, b**), or by passing through a column of silica gel using petroleum ether (b.p. 60–90 °C) as an eluent (**5a, b, c, f**), rejecting the first 50 ml which contain the excess phenyl isothiocyanate. To isolate **5h**, the whole reaction mixture is quenched with methanol, whereupon the product precipitates.

Method B:

Unsymmetrical N,N′-*Diarylthioureas* (**3**): A mixture of the aniline **2** (10 mmol) and phenyl isothiocyanate (**1**, R = H; 1.49 g, 11 mmol) is left at room temperature for 2 h, whereupon colorless crystals of the thiourea **3** precipitate. After quenching with petroleum ether (20 ml) and filtration of the mixture, product **3** is obtained in practically quantitative yield.

Substituted Aryl Isothiocyanates (**5**): The thiourea **3** is decomposed by heating in an oil bath for the time given in Table 1. The mixture is then cooled, quenched with petroleum ether (30 ml), and worked up as described under Method A.

Method C: The unsymmetrical thiourea **3** (10 mmol), obtained as in Method B, is heated with phenyl isothiocyanate (**1**, R = H; 1.62 g, 12 mmol) in an oil bath under reflux for the specified time (Table 1). A flaky crystalline sublimate of diphenylthiourea (**6**) appears in the condenser. The mixture is then treated as described under Method A.

2,4,6-Triphenylphenyl Isothiocyanate (5g) and 6-Anilino-2,4-diphenylphenanthridine (7):

2,4,6-Triphenylaniline (**2g**; 3.21 g, 10 mmol) and phenyl isothiocyanate (**1**, R = H; 2.97 g, 22 mmol) are heated under reflux for 6 h in an oil bath (190 °C) as in Method A. The resultant mixture is dissolved in dichloromethane (~ 50 ml) and this solution passed through a column of silica gel using petroleum ether (60 ≧ 90 °C) as eluent to remove excess **1**. Subsequent elution with petroleum ether/dichloromethane (9/1) affords product **5g** which is recrystallized from methanol; yield: 1.27 g (35%); m.p. 122–123 °C.

The column is then eluted with petroleum ether/dichloromethane (1/1; 200 ml) to give the yellow product **7** which is recrystallized from dichloromethane/methanol; yield: 1.61 g (38%); m.p. 163–164 °C.

$C_{31}H_{22}N_2$	calc.	C 88.12	H 5.25	N 6.63
(422.5)	found	87.82	5.48	6.78

M.S. (70 eV): m/e = 422 (100), M^+: 421 (85).

I.R. (KBr): ν = 3450, 3420, 3360 (NH); 1630 (C=N); δ = 1530 (NH) cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): δ = 6.9–8.8 ppm (m, H$_{arom}$).

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