Improved Procedures for the Preparation of Cycloalkyl-, Arylalkyl-, and Arylthioureas[1]

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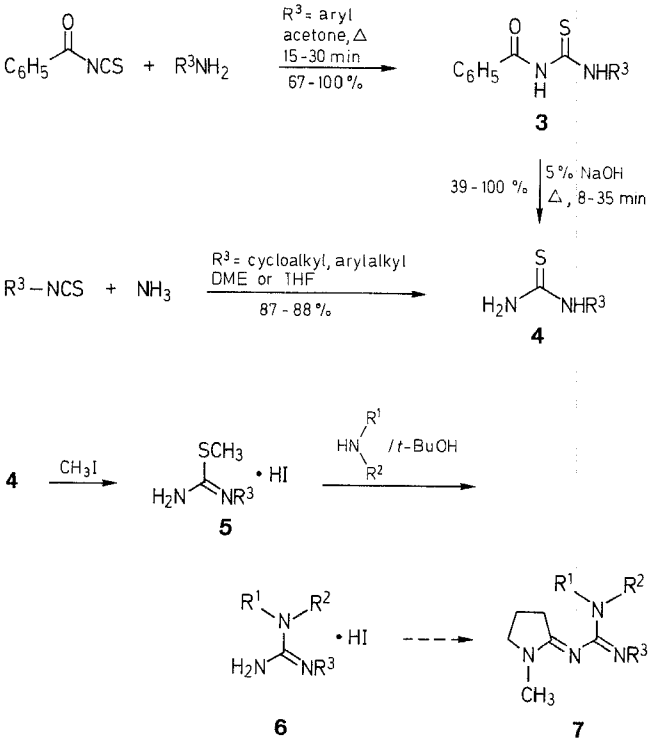
An improved procedure for the preparation of arylthioureas consists of the reaction of benzoyl isothiocyanate with anilines in acetone and debenzoylation of the resultant *N*-aryl-*N'*-benzoylthioureas with 5% aqueous sodium hydroxide. Bicycloalkylthioureas and *N*-(arylalkyl)thioureas (e.g., 9*H*-9-fluorenylthiourea) are directly prepared from the corresponding isothiocyanates and ammonia.

As part of a program for the synthesis of a novel series of hypoglycemic agents **7**[3] we required significant quantities of *N*-substituted thioureas **4** for conversion, via the corresponding methyl carbamimidothioate (*S*-methylpseudothiouronium) hydroiodides **5**, to penultimate intermediate guanidines **6** (see the following article). The reaction of benzoyl isothiocyanate (**1**) with anilines **2** and aqueous-alkaline cleavage of the resultant *N*-aryl-*N'*-benzoylthioureas **3** was used to prepare arylthioureas **4** (and a few heteroarylthioureas in an analogous manner) while cycloalkyl- and *N*-(arylalkyl)thioureas were directly prepared from the corresponding isothiocyanates and ammonia. Our improvements in the conditions for the preparation of arylthioureas constitute the main portion of this paper.



Arylthioureas are often prepared by reaction of an appropriate aniline hydrochloride with a thiocyanate salt (usually ammonium) in water,[4,5] by ammonolysis of aryl isothiocyanates,[6] and by reaction of an aromatic amine hydrochloride with thiocyanate in an aromatic solvent, e.g., chlorobenzene.[7] Aqueous conditions appear to work in moderate to good yields for certain anilines but often work poorly for others, e.g., 2,6-dichloroaniline. Although ammonolysis of aryl isothiocyanates to form arylthioureas works well, preparation of the required isothiocyanates in high-boiling aromatic solvents often proceeds in poor yield as do reactions of aromatic amine hydrochlorides with thiocyanate to form thioureas in the same types of solvents. Reactions in aromatic solvents usually afford mixtures of isothiocyanate, arylthiourea, and diarylthiourea.[7] Thiophosgene is also used too prepare aryl isothiocyanates; however, this reagent does not react well with anilines bearing 2,6-dihalo (Br, Cl) substituents.[6,7] None of the above methods appear to be adequate for preparation of a wide variety of ring-substituted arylthioureas.

Thus, a more broadly applicable, higher-yielding route to arylthioureas **4** was desirable. A detailed procedure[9] (based on Ref. 8) for the preparation of phenylthiourea **4** ($R^3 = C_6H_5$) allegedly required the use of rigorously dried, freshly distilled acetone for the *in situ* generation of benzoyl isothiocyanate (**1**; 1 mol equiv), which is then allowed to react with aniline to form *N*-benzoyl-*N'*-phenylthiourea **3**. Hydrolysis of the crude **3** in boiling aqueous sodium hydroxide (10%) gave crude phenylthiourea in 85% yield (76% purified). We have found that the burdensome requirement for rigorously dried, freshly distilled acetone is unnecessary. The use of excess amounts (usually ~ 10–50%) of the inexpensive **1** obviated the necessity for dry acetone and lead to improved yields of **3** as well. In those instances where **1** and anilines **2** were allowed to react in equimolecular portions, yields of benzoylthioureas **3** averaged several percent lower (cf. Table 1, entries 2, 5, 13, 16, 27, etc.). In addition, *boiling aqueous sodium hydroxide is often much too vigorous to allow isolation of the desired thioureas in high yields.* In fact, for the synthesis of those benzoylthioureas wherein R^3 is phenyl with an electron-withdrawing substituent (e.g., 4-NO_2 or 4-CF_3), the use of 5% aqueous sodium hydroxide is recommended. Using 12% (3N) aqueous sodium hydroxide at 75–85°C over 5–7 min, 4-trifluoromethylphenylthiourea had earlier been obtained in only 64% yield.[4] We obtained a 90% yield of this product using 5% aqueous sodium hydroxide at 80–85°C for 12 minutes (Table 2, entry 8). Most other substituents, however, are amenable to 10% sodium hydroxide. We have significantly reduced the temperature for *all* hydrolyses to ~ 75–85°C, although occasional excursions above and below this temperature range occurred. In general, mild phenyl ring-deactivating substituents, such as halo, and ring-activating substituents (OH, OR, alkyl, etc.) are more tolerant of higher temperatures and longer hydrolysis times. Using our conditions we obtained 2,6-dichlorophenylthiourea in an *overall* yield of 96% (Tables 1 and 2, entry 28), whereas an only 60% yield had been obtained using boiling sodium hydroxide.[10] 2,6-Dichlorophenylthiourea has been prepared in only 32% yield directly from 2,6-dichloroaniline hydrochloride and ammonium thiocyanate in water[11] (repeated with identical results in our hands). Whereas 4-nitrophenylthiourea could not be isolated by hydrolysis of the corresponding benzoylthiourea in boiling aqueous sodium hydroxide,[12] we obtained this compound in yields of 39–46% (several runs; Table 2, entry 25); this example thus illustrates the general value of our modifications.

In Ref. 12 this specific problem was overcome by substituting 4-nitrobenzoyl isothiocyanate for **1**; the resulting *N*-(4-nitrobenzoyl-*N'*-(4-nitrophenyl)thiourea reportedly hydrolyzed in

Table 1. *N*-Aryl-*N'*-benzoylthioureas **3** Prepared

Entry	Ar	mol NH_4SCN	mol C_6H_5COCl	mol $ArNH_2$	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c] or Lit. mp (°C)
1	C_6H_5	0.3	0.26	0.2	97	147.5–148.5 (*i*-PrOH)	148[14]
2	4-FC_6H_4	1.1	1.0	1.0	86	127–128 (acetone)	128.129.5[15]
3	2-ClC_6H_4	1.1	1.1	1.0	91	144–146 (acetone)	147–148[8]
4	3-ClC_6H_4	0.3	0.275	0.25	86	127.5–128 (MeOH/H_2O)	127–128[15]
5	4-ClC_6H_4	1.1	1.0	1.0	79	140–140.5 (EtOH)	140–141.5[15]
6	2-BrC_6H_4	0.96	0.87	0.58	95	137–138.5	138[12]
7	3-$CF_3C_6H_4$	0.3	0.26	0.2	93	114.5–115.5 (*i*-PrOH)	$C_{15}H_{11}F_3N_2OS$[c] (324.3)
8	4-$CF_3C_6H_4$	0.25	0.22	0.17	95	135–137 (EtOH)	$C_{15}H_{11}F_3N_2OS$[c,d,e] (324.3)
9	2-$CH_3C_6H_4$	1.1	1.05	1.0	87	119–121 (acetone)	117[16]
10	3-$CH_3C_6H_4$	1.5	1.4	1.0	96	126–128	118–119[17]
11	4-$CH_3C_6H_4$	1.3	1.2	1.0	>95	–[i]	158–159[16]
12	2-$C_2H_5C_6H_4$	0.91	0.87	0.83	97	95–97	$C_{16}H_{16}N_2OS$[f] (284.4)
13	4-$C_2H_5C_6H_4$	0.91	0.83	0.83	81	110–111 (MeOH/EtOH)	$C_{16}H_{16}N_2OS$[e] (284.4)
14	2-[H_2C=$C(CH_3)$]C_6H_4	0.62	0.56	0.38	95	123–124 (acetone)	$C_{17}H_{16}N_2OS$[f] (296.4)
15	2-(*i*-C_3H_7)C_6H_4	1.22	1.11	0.74	81	143–145 (acetone)	$C_{17}H_{18}N_2OS$[f] (298.4)
16	4-(*i*-C_3H_7)C_6H_4	0.81	0.74	0.74	67	95–96 (MeOH/EtOH)	$C_{17}H_{18}N_2OS$[f] (298.4)
17	4-(*t*-C_4H_9)C_6H_4	0.25	0.22	0.17	99	117–119 (polymorph), 131.5–132.5 (MeOH/*t*-BuOH)	$C_{18}H_{20}N_2OS$[e] (312.4)
18	4-OHC_6H_4	0.92	0.84	0.55	99	167–169 (MeOH/H_2O)	171–172[8]
19	2-$OCH_3C_6H_4$	0.6	0.55	0.50	88	153.5–155 (acetone)	154.5–155[15]
20	3-$OCH_3C_6H_4$	1.3	1.2	0.8	91	102–108 (crude) (*t*-BuOH/MeOH)	109–110.5[15]
21	4-$CH_3OC_6H_4$	1.05	1.0	1.0	83	150–154 (crude) (acetone)	155–156.5[15]
22	3-($C_6H_5CH_2O$)C_6H_4	0.29	0.28	0.25	99	139–140.5 (MeOH)	$C_{21}H_{18}N_2O_2S$[e] (362.4)
23	4-($C_6H_5CH_2O$)C_6H_4	0.35	0.32	0.31	86	130–135 (crude)	$C_{21}H_{18}N_2O_2S$[e] (362.4)
24	4-$CH_3SC_6H_4$	0.74	0.68	0.44	97	160–161 (acetone)	$C_{15}H_{14}N_2OS_2$[e] (302.4)
25	4-$NO_2C_6H_4$	0.55	0.55	0.5	77	182–184 (acetone)	$C_{14}H_{11}N_3O_3S$[e,g] (301.3)
26	4-[$(CH_3)_2N$]C_6H_4	0.99	0.91	0.59	88	173—174 (acetone)	173–173.5[18]
27	2,3-$Cl_2C_6H_3$	1.1	1.0	1.0	80	166–167 (EtOH)	$C_{14}H_{10}Cl_2N_2OS$[e] (325.2)
28	2,6-$Cl_2C_6H_3$	1.24	1.2	0.76	99	181–183 (crude) (MeOH)	178[19]
29	3,4-$Cl_2C_6H_3$	1.1	1.05	1.0	91	157.5–159 (acetone)	155–156[8]
30	2-Cl-4-$CH_3C_6H_3$	0.39	0.37	0.35	90	142–144 (crude)	$C_{15}H_{13}ClN_2OS$[f] (304.8)
31	3-Cl-2-$CH_3C_6H_3$	1.1	1.01	1.0	80	153–154 (CH_2Cl_2/Et_2O)	$C_{15}H_{13}ClN_2OS$[c,h] (304.8)
32	3-Cl-4-$CH_3C_6H_3$	0.62	0.56	0.38	100	138–140 (acetone)	$C_{15}H_{13}ClN_2OS$[f] (304.8)
33	4-Cl-2-$CH_3C_6H_3$	1.17	1.06	0.71	100	148–149 (acetone)	$C_{15}H_{13}ClN_2OS$[e] (304.8)
34	5-Cl-2-$CH_3C_6H_3$	0.78	0.75	0.71	93	152–153 (crude)	$C_{15}H_{13}ClN_2OS$[e] (304.8)
35	5-Cl-2-$CH_3OC_6H_3$	1.15	1.1	1.0	84	161–161.5 (acetone/MeOH)	$C_{15}H_{13}ClN_2O_2S$[e] (320.8)
36	2-Cl-4-($C_6H_5CH_2O$)C_6H_3	1.12	1.03	1.0	79	131.5–133 (acetone)	$C_{21}H_{17}ClN_2O_2S$[e] (396.9)
37	2,3-$(CH_3)_2C_6H_3$	0.83	0.82	0.82	84	156–157 (*t*-BuOH/MeOH)	$C_{16}H_{16}N_2OS$[e] (284.4)
38	2,4-$(CH_3)_2C_2H_3$	0.62	0.56	0.38	–[i]	104–106 (acetone)	$C_{16}H_{16}N_2OS$[e] (284.4)
39	2,5-$(CH_3)_2C_6H_3$	1.36	1.24	0.83	89	130–132 (acetone)	$C_{16}H_{16}N_2OS$[e] (284.4)
40	3,4-$(CH_3)_2C_6H_3$	0.88	0.8	0.8	85	129–130 (acetone)	$C_{16}H_{16}N_2OS$[e] (284.4)
41	3,5-$(CH_3)_2C_6H_3$	0.3	0.26	0.2	87	126–126.5 (*i*-PrOH)	$C_{16}H_{16}N_2OS$[e] (284.4)
42	3,4-$(CH_2)_3C_6H_3$	1.24	1.13	0.75	100	129–131 (acetone)	$C_{17}H_{16}N_2OS$[f] (296.4)
43	3,4-$(OCH_3)_2C_6H_3$	0.55	0.5	0.33	93	133–134	$C_{16}H_{16}N_2O_3S$[e] (316.4)
44	3,4-$(OCH_2O)C_6H_3$	0.77	0.7	0.65	76	159–162	$C_{15}H_{12}N_2O_3S$[f] (300.3)
45	2,4,5-$(CH_3)_3C_6H_2$	1.1	1.0	1.0	70	114–116 (*i*-PrOH)	$C_{17}H_{18}N_2OS$[e] (298.4)
46	2,5-$(CH_3)_2$-4-$CH_3OC_6H_2$	0.35	0.35	0.33	89	164–165.5 (MeOH)	$C_{17}H_{18}N_2O_2S$[e] (314.4)
47	2-pyridinyl	0.51	0.5	0.5	75	137–139	142–143[13]
48	3-pyridinyl	1.1	1.0	1.0	77	168–170	167–168[13]
49	2-pyrimidinyl	1.1	1.0	1.0	–[i]	177–178	177–178[13,e]

[a] Yield of isolated product (unoptimized) based on the aniline **2** (Table 1) or benzoylthiourea **3** (Table 2).
[b] Uncorrected, measured on a Thomas-Hoover apparatus.
[c] Satisfactory microanalyses obtained: C ±0.33, H ±0.31, N ±0.25 (Tables 1 and 2).
[d] Ref. 4 reported this compound, but gave no mp data.
[e] See corresponding entry Table 2.
[f] Not analyzed. See corresponding entries in accompanying paper.
[g] Ref. 12 reported this compound, but gave no mp.
[h] C, calc. 59.11; found 58.62. The corresponding thiourea (Table 2, entry 31) gave a correct analysis.
[i] Not recorded.[e]

high yield to 4-nitrophenylthiourea. *N*-Benzoyl-*N'*-(3-pyridyl)-thiourea has earlier been prepared in only 18% yield.[13] We found that adding 3-aminopyridine to a cooled (5 °C) solution of **1** furnished this product in 77% yield. Alkaline hydrolysis at 80 °C provided 3-pyridinylthiourea in 87% yield (Table 2, entry 48). Using our conditions, we obtained 2-pyrimidinylthiourea (Table 2, entry 49) in an overall yield of 57% from 2-aminopyrimidine in comparison with the literature value of 43%.[13]

The benzoylthioureas **3** and thioureas **4** employed in this work are shown in Tables 1 and 2, respectively. In several instances, new compounds were not analyzed for CHN, but were sufficiently pure (TLC) for direct conversion to the corresponding methyl carbamimidothioate hydroiodides **5** and then to guanidines **6** which were characterized by C, H, N analyses (see succeeding paper). Guanidines **6** thus serve as suitable derivatives for characterization of precursors **3, 4** and **5**. Each of these reactions are conveniently carried out on a 1-mol scale in standard laboratory equipment. In less than one day, one usually may have in hand substantial quantities of the salts **5**, which are, in most instances, stable, conveniently stored crystalline solids useful for the preparation of a wide variety of guanidines **6**.

Isothiocyanates employed in this work were either purchased commercially or prepared by standard literature procedures (9*H*-fluoren-9-yl isothiocyanate from 9-amino-9*H*-fluorene by the method of Ref. 32 and *exo*-bicyclo[2.2.1]heptan-2-yl isothiocyanate by the method of Ref. 33). We have found 1,2-dimethoxyethane (DME) and THF to be the solvents of choice for conversion of 9-fluorenyl and *exo*-bicyclo [2.2.1]heptan-2-yl isothiocyanates to the corresponding thioureas by treatment with excess anhydrous ammonia.

N-Aryl-N'-benzoyl-thioureas 3 (R^3 = aryl); General Procedure:
Benzoyl chloride (1.1–1.4 mol) is added over 5 min to a freshly prepared solution (no external heat) of NH_4SCN (1.2–1.5 mol) in reagent-grade acetone (endothermic) and the mixture is heated under reflux for ~15 min. Heating is stopped and the appropriate aniline **2** (1 mol), either neat or in acetone, is added as rapidly as possible maintaining a vigorous reflux. Following the addition, the mixture is

Table 2. Arylthioureas **4** via Hydrolysis of *N*-Aryl-*N'*-benzoylthioureas **3**

Entry	mol of **3**	Liters of $NaOH/H_2O$ (% w/v)	Temperature Range (°C)	Hydrolysis Time (min)	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c] or Lit. mp (°C)
1	0.19	0.47 (10)	73–80	20	84	154.5–155.5 (*i*-PrOH)	152.5–153[9]
2	0.86	0.86 (10)	80–85	9	80	166–168 (*i*-PrOH)	163[20]
3	0.89	0.90 (10)	80–85	8	94	144.5–146.5 (acetone)	146–146.5[6]
4	0.22	0.52 (5)	75–80	20	90	140–140.5 (acetone/H_2O)	138.5–139[17]
5	0.53	0.5 (10)	85–95	9	88	176–178 (*i*-PrOH)	176–177[21]
6	0.58	0.6 (10)	80–85	8	89	130–132.5 (acetone/Et_2O/hexane)	125[22]
7	0.185	0.45 (5)	74–80	25	87	111–111.5 ($CHCl_3$/hexane)	104–106[4]
8	0.15	0.65 (5)	80–85	12	90[m]	143.5–146 (toluene)	140–142[4]
9	0.85	0.90 (10)	85–90	8	96	160.5–162.5 (acetone/MeOH)	160[23]
10	0.95	0.90 (10)	80	30	85	110–113 (EtOH/H_2O)	110.5–111.5[6]
11	1.0	1.0 (10)	70–83	15	–[l]	–	194[15]
12	0.79	0.8 (20)	85–87	10	90	142–145 (crude)	$C_9H_{12}N_2S^{f,k}$ (180.3)
13	0.67	0.67 (10)	~85	13	87	135–137 (*i*-PrOH)	138[24]
14	0.36	0.36 (10)	80–85	8	87	174–176 (acetone/Et_2O)	$C_{10}H_{12}N_2S^{f,k}$ (192.3)
15	0.58	0.58 (10)	80–85	8	99	133–135 (acetone/Et_2O/hexane)	$C_{10}H_{14}N_2S^{f,k}$ (194.3)
16	0.50	0.50 (10)	80–85	8	92	149–150 (*i*-PrOH)	134[24,e]
17	0.13	0.13 (10)	80–85	8	96	154–155 (*i*-PrOH)	158[7]
18	0.62	1.49 (5)	75–80	20	100[m]	213–214 (Et_2O wash)	214[25]
19	0.43	0.50 (10)	90–95	8	90	153–155 (acetone/H_2O)	148–149[22]
20	0.72	0.7 (7.5)	75–83	8	86	157–159 (acetone)	160[21]
21	0.82	1.0 (10)	80–90	8	95	212.5–214 (MeOH wash)	210–211[22]
22	0.244	0.25 (20)	75–80	23	99	139–140.5 (acetone)	$C_{14}H_{14}N_2OS^e$ (258.3)
23	0.22	0.48 (8)	65–98	20	83	193–195 (EtOH/H_2O)	$C_{14}H_{18}N_2O_2S^e$ (258.3)
24	0.43	0.88 (5)	60–70	35	100	190–191 (crude)	198–199[26]
25	0.133	0.32 (5)	75–80	7	39–46[m]	220–242 (dec) (acetone)	245[12]
26	0.53	1.26 (5)	60–75	35	82	193–194.5 (*t*-BuOH)	190[22]
27	0.80	0.80 (10)	~85	9	96	155–157 (crude)	148[27] (221.1)
28	0.67	0.51 (10)	84–88	10	97	156.5–159 (*t*-BuOH/Et_2O)	157–159[11]
29	0.90	1.0 (10)	90–95	9	90	199.5–203	203–204[8]
30	0.31	0.4 (20)	85–87	10	99	162–165 (crude)	$C_8H_9ClN_2S^{f,k}$ (200.7)
31	0.80	0.8 (10)	85	9	96	183–184 (*t*-BuOH/Et_2O)	$C_8H_9ClN_2S^e$ (200.7)
32	0.38	0.42 (10)	80–85	8	97	177–178 (acetone)	$C_8H_9ClN_2S^{f,k}$ (200.7)
33	0.71	0.68 (10)	80–85	8	100	173.5–175.5 (acetone)	175–177[28]
34	0.66	0.80 (20)	80–87	8	93	136–137 (crude)	138[24]
35	0.84	0.85 (10)	75–85	23	79	144–146.5 (*i*-PrOH)	$C_8H_9ClNO_2S^e$ (216.7)
36	0.01	0.03 (20)	80–90	8	93	173–177 (acetone)	$C_{14}H_{13}ClN_2OS^e$ (292.8)
37	0.69	0.69 (10)	80–85	9	95	208–210 (*i*-PrOH/Et_2O)	182[22]
38	0.37	0.42 (10)	80–85	8	97	179–182 (acetone/hexane)	181.5[6]
39	0.70	0.75 (10)	80–85	8	95	143–143.5 (acetone/hexane)	141[29]
40	0.68	0.68 (10)	~85	9	99	184–186 (DME/Et_2O)	181–182[30]
41	0.67	0.70 (10)	80–85	9	90	172–173 (*i*-PrOH)	$C_9H_{12}N_2S^{f,l}$ (180.3)
42	0.75	0.75 (10)	80–85	8	100	176–179 (acetone)	$C_{10}H_{12}N_2S^{f,k}$ (192.3)
43	0.30	0.30 (10)	50–80	18	98	234–242 (dec) (crude)	234[22]
44	0.48	1.0 (8)	70–90	30	96	209–211 (dec) (crude)	$C_8H_8N_2O_2S^{f,k}$ (196.2)
45	0.70	0.70 (10)	85	9	96	156–158 (*t*-BuOH/cyclohexane)	167.5–168[6]
46	0.31	0.30 (20)	80–90	9	95	228.5–229.5 (dec) (DMF)	$C_{10}H_{14}N_2OS^e$ (210.3)
47	0.37	0.37 (10)	80–89	10	88	145–147 (MeOH)	147–148[13]
48	0.86	0.86 (10)	80	15	87[m]	164–166 (crude)	166–167[13]
49	0.2	0.2 (10)	80–87	5	57 (overall)	260–265 (dec) (crude)	255–256[13]

Table 2. (continued)

Entry	Ar[j]	mol of **3**	Liters of $NaOH/H_2O$ (% w/v)	Temperature Range (°C)	Hydrolysis Time (min)	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c] or Lit. mp (°C)
50	4-(n-C_4H_9)C_6H_4	[n]				60	137–140 (EtOAc)	$C_{11}H_{16}N_2S$[f,k] (208.3)
51	*exo*-bicyclo[2.2.1]-heptan-2-yl	[m]				88	181–183 (crude)	$C_8H_{14}N_2S$[f,k,m]
52	9*H*-fluoren-9-yl	[m]				87	205–207 (Et_2O)	$C_{14}H_{12}N_2S$[f,l,m] (240.3)
53	$-CH(C_6H_5)_2$	[m]				79	187–189 (*i*-PrOH)	186–187[31]

[a–i] See Table 1.
[j] For entries 1–49, see Ar in the corresponding entry in Table 1.
[k] See corresponding entry(s) in the accompanying paper (Table 2).
[l] See corresponding entry in the accompanying paper (Table 1).
[m] See experimental.
[n] Prepared from the aniline hydrochloride and ammonium thiocyanate according to Ref. 5.

heated under reflux for 15 to 30 min, then poured onto excess cracked ice with vigorous stirring. The resulting solid is collected and liberally washed with H_2O, followed by cold H_2O/MeOH (1:1) or MeOH. The products are often sufficiently pure to be used directly for hydrolysis to the thioureas **4**.

***N*-Benzoyl-*N'*-(3-pyridyl)thiourea** (Table 1, entry 48):
A freshly prepared acetone solution of benzoyl isothiocyanate (1 mol) prepared from NH_4SCN (83.75 g, 1.1 mol) and benzoyl chloride (140.57 g, 1 mol) is cooled to 25 °C, filtered from NH_4Cl, and the filter cake washed with fresh acetone (2 × 50 mL). The combined filtrates are cooled to 5 °C and a solution of 3-aminopyridine (94.12 g, 1.0 mol) in acetone (400 mL) is added dropwise over 30 min. After stirring the mixture at 5–10 °C for 1 h, the product is collected, washed with a little cold acetone, and dried.

Base-Soluble Arylthioureas 4 (R^3 = Aryl); General Procedure:
The appropriate *N*-benzoylthiourea **3** (amount see Table 2) is added in one portion to a preheated (~ 80 °C) stirring solution of 5% aq. NaOH. After stirring at the temperature and time indicated in Table 2, the mixture is poured onto excess ice containing excess aq. HCl.

Work-up A (for 4-trifluoromethyl-, 4-hydroxy-, and 4-nitrophenylthiourea; Table 2, entries 8, 18, 25): The resulting coprecipitate of benzoic acid and product (in the case of 4-nitrophenylthiourea, a considerable amount of starting material is also present) are washed liberally with H_2O, then Et_2O to remove benzoic acid. Following isolation of crude 4-nitrophenylthiourea, trituration with DMSO selectively dissolves the desired product. Filtration from unchanged *N*-benzoyl-*N'*-(4-nitrophenyl)thiourea, the dilution of hte filtrate with ice water furnishes the product containing a trace of starting material. Recrystallization as shown (Table 2, entry 25) gives pure 4-nitrophenylthiourea. The other two thioureas are essentially pure after the Et_2O wash.

Work-up B (for all other arylthioureas): After the above described acidification, the pH is adjusted to ~ 8–8.5 with Na_2CO_3, $NaHCO_3$, or NH_4OH to remove benzoic acid. The products are collected, washed with H_2O, and dried. TLC systems commonly used are Silica Gel GF with toluene/Et_2O/MeOH (4:4:1), acetone/MeOH (9:1), toluene/MeOH (4:1), or toluene as eluting solvents. The benzoylthioureas routinely show R_f values higher than the corresponding thioureas.

Arylalkyl- and Cycloalkylthioureas; General Procedure:
Treatment of solutions of 9-fluorenyl and *exo*-bicyclo[2.2.1]heptan-2-yl isothiocyanates in DME or THF saturated with anhydrous NH_3 gives, after solvent removal and recrystallization, the pure thioureas (Table 2, entries 51, 52). These reactions are monitored by TLC.

Benzhydrylthiourea (Table 2, entry 53):
This compound is prepared directly from benzhydrylamine hydrochloride by the method of Ref. 31; yield: 79%.

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