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Received November 6, 1989

The title compounds **3** were synthesized in one step from bisdithiocarbamates **2**, and their structures were confirmed by two independent syntheses. Alkylation and hydrolysis of **3** gives 3,3'-arylenebis(2,4-dioxo-1,2,3,4-tetrahydroquinazolines) **8**.

J. Heterocyclic Chem., **27**, 1345 (1990).

4-Oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines are well-known compounds, the synthesis of which has usually been carried out by the reaction of anthranilic acids, or derivatives thereof, with thioureas, carbon disulfide and isothiocyanates [2].

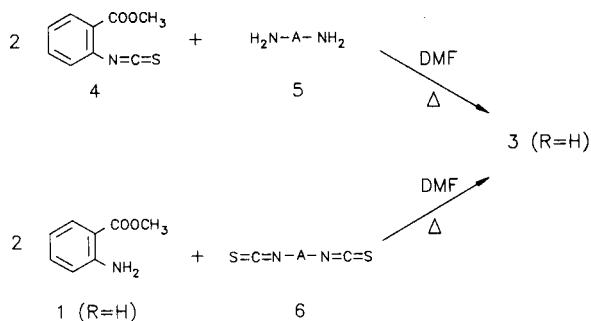
A few years ago we reported [3] that the reaction of anthranilic acids with methyl *N*-aryldithiocarbamates afforded the above-mentioned heterocycles in medium to good yields and later on we extended the annelation of the 4-oxo-2-thioxopyrimidine ring to other systems, such as pyridine [4], pyrazole [5] and thiophene [5].

In this paper, and as a continuation of our interest in bisdithiocarbamic acid esters [1], we report that the reaction of methyl anthranilates **1** with dimethyl *N,N'*-arylenebisdithiocarbamates **2** affords title compounds **3** in moderate to good yields (Scheme I). The reactions were carried out by simply refluxing a 2:1 mixture of the reactants in DMF. The desired products precipitated on cooling, thus allowing their isolation in very high purity. Yields were in the range of 50-75% (Table 1) except for compounds **3a**

(those derived from *p*-phenylenediamine) which were lower. This was ascribed to the enhanced mutual influence of the two nitrogen atoms directly linked to the phenylene

It is noteworthy that the reaction of anthranilic acids themselves with compounds **2** did not afford pure compounds **3**, but a mixture of **3** and the corresponding 3,3'-arylenebis(2,4-dioxo-1,2,3,4-tetrahydroquinazoline) [6] as detected by ir spectroscopy. This compound resulted from a competitive nucleophilic attack of the COOH group on the intermediate thiourea (hydrogen sulfide was evolved) followed by a benzoxazinone → quinazolinone rearrangement [5]. This behaviour was different from that described [3] for simple methyl *N*-aryldithiocarbamates, and we were forced to use methyl esters **1** instead of the free acids.

Scheme II

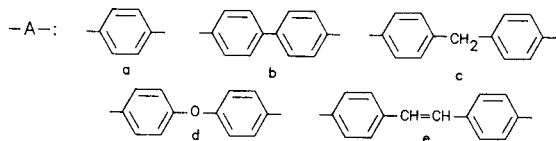
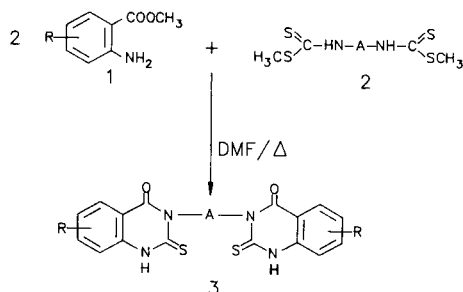


-A- as in Scheme I

In order to confirm the proposed structures, two independent syntheses of compounds **3** (R = H), chosen as models, were carried out (Scheme II). Both the reaction of methyl 2-isothiocyanatobenzoate **4** [7] with arylenediamines **5** and the reaction of methyl anthranilate with arylenediisothiocyanates **6** [8] in refluxing DMF did afford the corresponding bisquinazolines **3**, identical in every respect to the compounds prepared according to Scheme I.

Not unexpectedly, yields were almost identical by both routes (53-63%), since the reactions presumably pro-

Scheme I



R = H, 6-CH₃, 6-Cl, 7-Cl, 7-NO₂

Table 1
3,3'-Arylenebis(4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines)

Compound	R	mp (°C) [a]	Yield (%)		
			Method A [b]	Method B [c]	Method C [d]
3a	H	>300 [e]	41	55	53
	6-CH ₃	>300	39		
	6-Cl	>300	36		
	7-Cl	>300	35		
	7-NO ₂	>300	21		
3b	H	>300 [f]	70	63	62
	6-CH ₃	>300	73		
	6-Cl	>300	65		
	7-Cl	254-255	67		
	7-NO ₂	276-278	52		
3c	H	>300	71	59	59
	6-CH ₃	>300	68		
	6-Cl	>300	50		
	7-Cl	272-274	54		
	7-NO ₂	264-266	48		
3d	H	>300	68	60	61
	6-CH ₃	>300	49		
	6-Cl	>300	65		
	7-Cl	>300	69		
	7-NO ₂	284-286	50		
3e	H	>300	63	62	60

[a] All compounds were recrystallized from DMF. [b] From 1 and 2. [c] From 4 and 5. [d] From 1 and 6. [e] Lit [9] 310°. [f] Lit [9] 300-301°.

ceeded through the same thioureido intermediate.

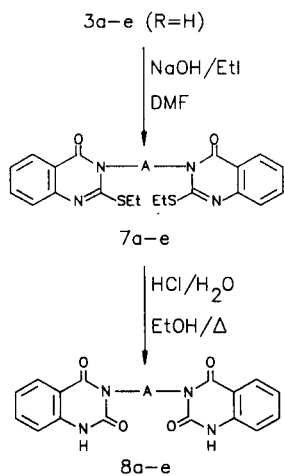
Compounds **3** were very sparingly soluble in all solvents normally used in ¹H-nmr spectroscopy, including TFA. Nevertheless, the spectra of products **3a-e** (R = H) and **3a** (R = 6-CH₃) were taken in a 200 MHz apparatus and showed, apart from the signals of the A group, a singlet at δ 13.0 ppm (N-H), and the peaks of the quinazoline ring protons which, in all cases, appeared in the order δ H₅ > δ H₇ > δ H₆, H₈, which was unambiguously ascertained by comparison with the spectrum of the 6-CH₃ derivative.

In their ir spectra, compounds **3** displayed a strong band between 1720-1660 cm⁻¹, attributable to ν (C₄ = O).

Alkylation of **3a-e** (R = H) with ethyl iodide in a basic medium provided the S-ethyl derivatives **7a-e** in high yields (Table 2) (Scheme III), and acidic hydrolysis of the latter gave the corresponding 3,3'-arylenebis(2,4-dioxo-1,2,3,4-tetrahydroquinazolines) **8** (Table 3).

These compounds were identical to those obtained [6] by an independent and shorter route which, nevertheless, failed to give **8e**.

Scheme III



-A- as in Scheme I

Table 2
3,3'-Arylenebis(2-ethylthio-4-oxo-3,4-dihydroquinazolines)

Compound	mp (°C) [a]	Yield (%)
7a	>300	85
7b	>300	91
7c	296-298	86
7d	294-296	87
7e	>300	83

[a] All compounds were recrystallized from chloroform.

Table 3
3,3'-Arylenebis(2,4-dioxo-1,2,3,4-tetrahydroquinazolines)

Compound	mp (°C) [a]	Yield (%)
8a	>300	78
8b	>300	80
8c	>300	76
8d	>300	82
8e	>300	73

[a] All compounds were recrystallized from DMSO.

To sum up, we prepared 3,3'-arylenebis(4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines) **3** in one step, and in medium to good yields. They were also converted into the bis(2,4-dioxo) compounds **8**.

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer FT 1600 instrument. The ¹H nmr spectra were recorded on a Bruker WP 80 CW and a Varian XL-200 spectrometer with TMS as internal reference.

Synthesis of 3,3'-Arylenebis(4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines) **3**.

General Procedures.

Method A.

A mixture of the corresponding methyl anthranilate **1** (5.0 mmoles) and dimethyl *N,N'*-arylenebisdithiocarbamate **2** (2.5 mmoles) in dimethylformamide (15 ml) was refluxed for 48 hours. The mixture was cooled in an ice-bath and the precipitate thus obtained was filtered off and was washed first with water, then with ethanol and finally with ether and dried to give pure compounds **3**. A second fraction was obtained by addition of water to the filtrate until precipitation. This solid was purified either by washing it with hot ethanol and cold DMF or by recrystallization from DMF.

Method B.

A mixture of methyl 2-isothiocyanatobenzoate **4** (0.97 g, 5.0 mmoles) and the corresponding arylenediamine **5** (2.5 mmoles) in DMF (30 ml) was kept at 60-80° for 2 hours and then refluxed for 24 hours. The mixture was cooled and the solid which precipitated was isolated by suction, washed with cold DMF and methanol and dried. A second fraction was obtained and purified as described in method A.

Method C.

A mixture of methyl anthranilate **1** (R = H) (0.76 g, 5.0 mmoles) and the corresponding arylenediisothiocyanate **6** (2.5 mmoles) in DMF (25 ml) was kept at 60-80° for 2 hours and then refluxed for 24 hours. After cooling, compounds **3** were isolated and purified as described in method B.

3,3'-(1,4-Phenylene)bis(4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3a**, R = H).

This compound had ir: 1680 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 13.0 (s, 1H), 8.0 (d, 1H, J = 8), 7.85-7.7 (m, 1H), 7.5-7.3 (m, 4H).

Anal. Calcd. for C₂₂H₁₄N₄O₂S₂: C, 61.38; H, 3.28; N, 13.01. Found: C, 61.30; H, 3.31; N, 13.15.

3,3'-(1,4-Phenylene)bis(6-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3a**, R = 6-CH₃).

This compound had ir: 1720 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 13.0 (s, 1H), 7.8 (s, 1H), 7.6 (m, 1H), 7.4 (d, 1H, J = 8), 7.3 (s, 2H), 2.3 (s, 3H).

Anal. Calcd. for C₂₄H₁₈N₄O₂S₂: C, 62.86; H, 3.96; N, 12.22. Found: C, 62.72; H, 4.04; N, 12.35.

3,3'-(1,4-Phenylene)bis(6-chloro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3a**, R = 6-Cl).

This compound had ir: 1720 cm⁻¹.

Anal. Calcd. for C₂₂H₁₂Cl₂N₄O₂S₂: C, 52.91; H, 2.42; N, 11.22. Found: C, 52.73; H, 2.52; N, 11.05.

3,3'-(1,4-Phenylene)bis(7-chloro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3a**, R = 7-Cl).

This compound had ir: 1670 cm⁻¹.

Anal. Calcd. for C₂₂H₁₂Cl₂N₄O₂S₂: C, 52.91; H, 2.42; N, 11.22. Found: C, 52.73; H, 2.37; N, 11.40.

3,3'-(1,4-Phenylene)bis(7-nitro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3a**, R = 7-NO₂).

This compound had ir: 1710, 1520, 1350 cm⁻¹.

Anal. Calcd. for C₂₂H₁₂N₆O₆S₂: C, 50.77; H, 2.32; N, 16.15. Found: C, 50.83; H, 2.14; N, 16.07.

3,3'-(4,4'-Biphenylene)bis(4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3b**, R = H).

The compound had ir: 1690 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 13.0 (s, 1H), 8.0 (d, 1H, J = 8), 7.9-7.7 (m, 3H), 7.5-7.3 (m, 4H).

Anal. Calcd. for C₂₈H₁₈N₄O₂S₂: C, 66.39; H, 3.58; N, 11.06. Found: C, 66.58; H, 3.66; N, 10.88.

3,3'-(4,4'-Biphenylene)bis(6-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3b**, R = 6-CH₃).

This compound had ir: 1670 cm⁻¹.

Anal. Calcd. for C₃₀H₂₂N₄O₂S₂: C, 67.40; H, 4.15; N, 10.48. Found: C, 67.61; H, 4.24; N, 10.62.

3,3'-(4,4'-Biphenylene)bis(6-chloro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3b**, R = 6-Cl).

This compound had ir: 1680 cm⁻¹.

Anal. Calcd. for C₂₈H₁₆Cl₂N₄O₂S₂: C, 58.44; H, 2.80; N, 9.74. Found: C, 58.22; H, 2.71; N, 9.88.

3,3'-(4,4'-Biphenylene)bis(7-chloro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3b**, R = 7-Cl).

This compound had ir: 1720 cm⁻¹.

Anal. Calcd. for C₂₈H₁₆Cl₂N₄O₂S₂: C, 58.44; H, 2.80; N, 9.74. Found: C, 58.50; H, 2.94; N, 9.69.

3,3'-(4,4'-Biphenylene)bis(7-nitro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3b**, R = 7-NO₂).

This compound had ir: 1690, 1540, 1360 cm⁻¹.

Anal. Calcd. for C₂₈H₁₆N₆O₆S₂: C, 56.37; H, 2.70; N, 14.09. Found: C, 56.46; H, 2.79; N, 14.12.

3,3'-(4,4'-Methylenediphenylene)bis(4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3c**, R = H).

This compound had ir: 1665 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 13.0 (s, 1H), 7.9 (d, 1H, J = 8), 7.8-7.7 (m, 1H), 7.5-7.1 (m, 6H), 4.0 (s, 1H).

Anal. Calcd. for C₂₉H₂₀N₄O₂S₂: C, 66.90; H, 3.87; N, 10.76. Found: C, 67.01; H, 3.97; N, 10.60.

3,3'-(4,4'-Methylenediphenylene)bis(6-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3c**, R = 6-CH₃).

This compound had ir: 1690 cm⁻¹.

Anal. Calcd. for C₃₁H₂₄N₄O₂S₂: C, 67.86; H, 4.41; N, 10.21. Found: C, 67.73; H, 4.44; N, 10.34.

3,3'-(4,4'-Methylenediphenylene)bis(6-chloro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3c**, R = 6-Cl).

This compound had ir: 1670 cm^{-1} .

Anal. Calcd. for $\text{C}_{29}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_2\text{S}_2$: C, 59.09; H, 3.08; N, 9.50. Found: C, 59.17; H, 3.07; N, 9.58.

3,3'-(4,4'-Methylenediphenylene)bis(7-chloro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3c**, R = 7-Cl).

This compound had ir: 1700 cm^{-1} .

Anal. Calcd. for $\text{C}_{29}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_2\text{S}_2$: C, 59.09; H, 3.08; N, 9.50. Found: C, 58.99; H, 2.99; N, 9.64.

3,3'-(4,4'-Methylenediphenylene)bis(7-nitro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3c**, R = 7-NO₂).

This compound had ir: 1690 cm^{-1} .

Anal. Calcd. for $\text{C}_{29}\text{H}_{16}\text{N}_6\text{O}_5\text{S}_2$: C, 57.04; H, 2.97; N, 13.76. Found: C, 56.97; H, 3.02; N, 13.83.

3,3'-(4,4'-Oxydiphenylene)bis(4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3d**, R = H).

This compound had ir: 1690 cm^{-1} ; ¹H-nmr (DMSO-d₆): δ 13.0 (s, 1H), 8.0 (d, 1H, J = 7), 7.9-7.7 (m, 1H), 7.5-7.2 (m, 4H), 7.1 (d, 2H, J = 8).

Anal. Calcd. for $\text{C}_{28}\text{H}_{18}\text{N}_4\text{O}_3\text{S}_2$: C, 64.35; H, 3.47; N, 10.72. Found: C, 64.15; H, 3.58; N, 10.70.

3,3'-(4,4'-Oxydiphenylene)bis(6-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3d**, R = 6-CH₃).

This compound had ir: 1670 cm^{-1} .

Anal. Calcd. for $\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_3\text{S}_2$: C, 65.44; H, 4.03; N, 10.17. Found: C, 65.23; H, 4.10; N, 10.28.

3,3'-(4,4'-Oxydiphenylene)bis(6-chloro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3d**, R = 6-Cl).

This compound had ir: 1660 cm^{-1} .

Anal. Calcd. for $\text{C}_{28}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_3\text{S}_2$: C, 56.86; H, 2.73; N, 9.47. Found: C, 56.99; H, 2.85; N, 9.39.

3,3'-(4,4'-Oxydiphenylene)bis(7-chloro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3d**, R = 7-Cl).

This compound had ir: 1670 cm^{-1} .

Anal. Calcd. for $\text{C}_{28}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_3\text{S}_2$: C, 56.86; H, 2.73; N, 9.47. Found: C, 56.68; H, 2.83; N, 9.42.

3,3'-(4,4'-Oxydiphenylene)bis(7-nitro-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3d**, R = 7-NO₂).

This compound had ir: 1660, 1520, 1350 cm^{-1} .

Anal. Calcd. for $\text{C}_{28}\text{H}_{16}\text{N}_6\text{O}_7\text{S}_2$: C, 54.90; H, 2.63; N, 13.72. Found: C, 54.93; H, 2.80; N, 13.83.

3,3'-(4,4'-Vinylenediphenylene)bis(4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline) (**3e**, R = H).

This compound had ir: 1700 cm^{-1} ; ¹H-nmr (DMSO-d₆): δ : 13.0 (s, 1H), 8.0 (d, 1H, J = 8), 7.9-7.6 (m, 3H), 7.5-7.2 (m, 5H).

Anal. Calcd. for $\text{C}_{30}\text{H}_{20}\text{N}_4\text{O}_2\text{S}_2$: C, 67.65; H, 3.78; N, 10.52. Found: C, 67.53; H, 3.74; N, 10.46.

Synthesis of 3,3'-arylenebis(2-ethylthio-4-oxo-3,4-dihydroquinazolines) **7**.

General Procedure.

To a suspension of the corresponding compound **3** (1.0 mmoles) in DMF (15 ml), 5M aqueous sodium hydroxide (0.4 ml, 2.0 mmoles) was added and the mixture was stirred until a clear solution was obtained (approximately one hour). After the addi-

tion of ethyl iodide (0.312 gr, 2.0 mmoles) stirring at room temperature was continued for 4 hours and the resulting precipitate was filtered off, washed with water and dried. A second fraction was obtained by addition of water to the filtrate. Compounds **7** were recrystallized from chloroform.

3,3'-(1,4-Phenylene)bis(2-ethylthio-4-oxo-3,4-dihydroquinazoline) (**7a**).

This compound had ir: 1690 cm^{-1} ; ¹H-nmr (deuteriochloroform): δ 8.2 (d, 1H, J = 8), 7.9-7.2 (m, 5H), 3.2 (q, 2H, J = 7), 1.4 (t, 3H, J = 7).

Anal. Calcd. for $\text{C}_{26}\text{H}_{22}\text{N}_4\text{O}_2\text{S}_2$: C, 64.18; H, 4.56; N, 11.51. Found: C, 64.00; H, 4.44; N, 11.60.

3,3'-(4,4'-Biphenylene)bis(2-ethylthio-4-oxo-3,4-dihydroquinazoline) (**7b**).

This compound had ir: 1680 cm^{-1} ; ¹H-nmr (deuteriochloroform): δ 8.2 (d, 1H, J = 8), 7.9-7.2 (m, 7H), 3.2 (q, 2H, J = 7), 1.4 (t, 3H, J = 7).

Anal. Calcd. for $\text{C}_{32}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$: C, 68.30; H, 4.66; N, 9.96. Found: C, 68.32; H, 4.65; N, 10.15.

3,3'-(4,4'-Methylenediphenylene)bis(2-ethylthio-4-oxo-3,4-dihydroquinazoline) (**7c**).

This compound had ir: 1700 cm^{-1} ; ¹H-nmr (deuteriochloroform): δ 8.2 (d, 1H, J = 8), 7.9-7.0 (m, 7H), 4.2 (s, 1H), 3.1 (q, 2H, J = 7), 1.4 (t, 3H, J = 7).

Anal. Calcd. for $\text{C}_{33}\text{H}_{28}\text{N}_4\text{O}_2\text{S}_2$: C, 68.73; H, 4.89; N, 9.71. Found: C, 68.82; H, 5.05; N, 9.68.

3,3'-(4,4'-Oxydiphenylene)bis(2-ethylthio-4-oxo-3,4-dihydroquinazoline) (**7d**).

This compound had ir: 1690 cm^{-1} ; ¹H-nmr (deuteriochloroform): δ 8.2 (d, 1H, J = 8), 7.8-6.9 (m, 7H), 3.1 (q, 2H, J = 7), 1.3 (t, 3H, J = 7).

Anal. Calcd. for $\text{C}_{32}\text{H}_{26}\text{N}_4\text{O}_3\text{S}_2$: C, 66.42; H, 4.53; N, 9.68. Found: C, 66.47; H, 4.54; N, 9.50.

3,3'-(4,4'-Vinylenediphenylene)bis(2-ethylthio-4-oxo-3,4-dihydroquinazoline) (**7e**).

This compound had ir: 1680 cm^{-1} ; ¹H-nmr (deuteriochloroform): δ 8.2 (d, 1H, J = 8); 7.9-6.9 (m, 8H), 3.1 (q, 2H, J = 7), 1.3 (t, 3H, J = 7).

Anal. Calcd. for $\text{C}_{34}\text{H}_{28}\text{N}_4\text{O}_2\text{S}_2$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.48; H, 4.66; N, 9.54.

Hydrolysis of compounds **7**. Synthesis of 3,3'-arylenebis(2,4-dioxo-1,2,3,4-tetrahydroquinazolines) **8**.

To a suspension of the corresponding compound **7** (1 mmoles) in ethanol (15 ml), 6N hydrochloric acid (5 ml) was added and the mixture was refluxed for 6 hours. After cooling, the resulting solid was filtered off and washed with water, ethanol and ether and dried. The compounds thus obtained were recrystallized from DMSO. They were identical in every respect to the compounds prepared independently either from potassium anthranilates or from 2-isocyanatobenzoyl chloride [1].

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