A Facile Synthesis of Unsymmetrical Heterocyclic Azines by Cyclodesulfurization: Reaction of Methyl Arylalkylidenehydrazinecarbodithioates with Diamines

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A new and facile synthesis of unsymmetrical heterocyclic azines is described. Methyl arylalkylidenehydrazinecarbodithioates, prepared by the condensation of ketones or aldehydes with methyl hydrazinecarbodithioate, were heated under reflux with various diamines in ethanol. Secondary diamines, such as *N,N'*-dimethylethylenediamine, *N,N'*-dimethyl-1,3-diaminopropane or *N,N'*-dimethyl-*o*-phenylenediamine, reacted smoothly with loss of hydrogen sulfide to give good yields of unsymmetrical azines. However, primary diamines, such as ethylenediamine or *o*-phenylenediamine, and primary/secondary diamines, such as *N*-methylethylenediamine and *N*-methyl-1,3-diaminopropane gave, instead, only the corresponding uncyclized thiosemicarbazones. A cyclodesulfurization mechanism for azine formation is discussed.

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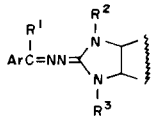
Unsymmetrical azines **1** containing N^1,N^3-dimethyl-2-imidazolidinylidene or N^1,N^3-dimethyl-1,3-dihydro-2*H*-benzimidazole-2-ylidene rings have been reported to inhibit the growth of murine tumors [1], to act as fluorescent brightening agents and photosensitizers [2,3]. Synthetic approaches to these unsymmetrical azines involve: a) condensation of appropriate aldehydes or ketones with 2-imidazolidinylidene hydrazone or 1,3-dihydro-2*H*-benzimidazol-2-ylidene hydrazone [1-3] or b) reaction of 1,1-dibromo-2,3-diazabutadienes [4,5] with diamines. These synthetic methods generally require a multiple step synthesis of the requisite hydrazones or dibromides.



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In this communication, we report a new and facile syn-

Table I

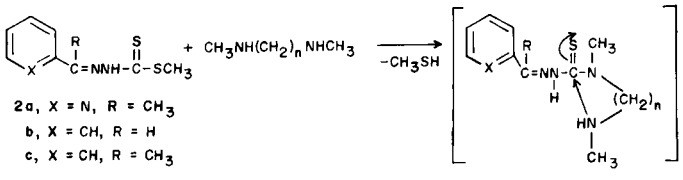
Condensation Products of **2a** with Diamines

Compound No.	Diamine	Mp °C	Yield %	Recrystallization Solvent	^{1}H-NMR, δ (ppm)
3a	$CH_3NHCH_2CH_2NHCH_3$	107-109	58	acetonitrile	2.48 (s, 3H), 3.13 (br s, 4H), 3.32 (s, 6H), 7.14 (m, 1H), 7.56 (m, 1H), 8.01 (d, 1H), 8.54 (m, 1H)
3b	$CH_3NH(CH_2)_3NHCH_3$	56-58	55	heptane/ethyl acetate	1.97 (q, 2H), 2.48 (s, 3H), 3.12 (s, 6H), 3.25 (t, 4H), 7.10 (m, 1H), 7.58 (m, 1H), 8.11 (m, 1H), 8.55 (m, 1H)
4b	$CH_3NH(CH_2)_2NH_2$	143-144	54	acetonitrile	2.39 (s, 3H), 2.48 (s, 3H), 2.91 (t, 2H, J = 5.8 Hz), 3.82 (t, 2H, J = 5.8 Hz), 7.29 (m, 1H), 7.72 (m, 1H), 8.00 (d, 1H, J = 8.1 Hz), 8.59 (m, 1H)
4c	$CH_3NH(CH_2)_3NH_2$	116-118	47	ethyl acetate/petroleum ether	1.83 (m, 2H), 2.38 (s, 3H), 2.44 (s, 3H), 2.80 (t, 2H, J = 5.85 Hz), 3.85 (t, 2H, J = 5.85 Hz), 4.93 (br s, 1H), 7.27 (m, 1H), 7.68 (m, 1H), 8.07 (d, 1H, J = 7.2 Hz), 8.59 (m, 1H), 9.10 (br s, 1H)
6a	$(NH_2CH_2)_2C(CH_3)_2$	183-185	45	acetonitrile	1.06 (s, 6H), 2.47 (s, 3H), 3.03 (d, 4H), 5.64 (br s, 1H), 6.51 (br s, 1H), 7.11 (m, 1H), 7.57 (m, 1H), 8.01 (d, 1H), 8.54 (m, 1H)
8	*o*-$C_6H_4(NH_2)_2$	186-187	40	chloroform/ethanol	2.48 (s, 3H), 3.82 (br s, 2H), 6.90 (m, 2H), 7.26 (m, 3H), 7.72 (m, 1H), 8.06 (d, 1H, J = 7.2 Hz), 8.60 (m, 1H), 8.98 (br s, 2H)
9	*o*-$C_6H_4(NHCH_3)_2$	115-117	35	cyclohexane	2.55 (s, 3H), 3.74 (s, 6H), 7.00 (m, 5H), 7.62 (m, 1H), 8.02 (d, 1H), 8.58 (d, 1H)

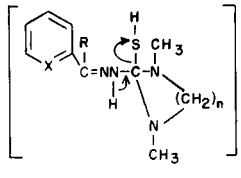
thesis of unsymmetrical azines by treatment of appropriate methyl arylalkylidenehydrazinecarbodithioates **2** with readily available diamines.

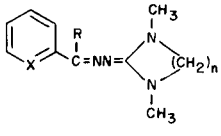
The synthesis of the key starting material, **2**, was achieved by the condensation of methyl hydrazinecarbodithioate with an appropriate aldehyde or ketone. The resulting methyl arylalkylidenehydrazinecarbodithioate was then heated with one equivalent of a diamine in refluxing ethanol for 12 hours. Under these conditions, secondary diamines, such as *N,N'*-dimethylethylenediamine or *N,N'*-dimethyl-1,3-diaminopropane reacted smoothly with methyl 3-[1-(2-pyridinyl)ethylidene]hydrazinecarbodithioate (**2a**) to give good yields of azine **3a** or **3b** (see Table I) with concomitant evolution of methyl mercaptan and hydrogen sulfide.

Scheme I



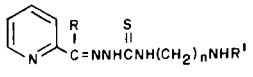
2a, X = N, R = CH_3
b, X = CH, R = H
c, X = CH, R = CH_3



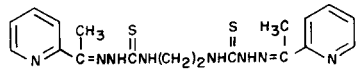


3a, X = N, R = CH_3, n = 2
b, X = N, R = CH_3, n = 3
c, X = CH, R = H, n = 2
d, X = CH, R = H, n = 3
e, X = CH, R = CH_3, n = 2
f, X = CH, R = CH_3, n = 3

Treatment of **2a** with the primary diamine, ethylenediamine, however, gave none of the desired azine. Instead, the corresponding mono- (**4a**) and bis-thiosemicarbazone (**5**) were obtained. The ratio of mono- to bis-thiosemicarbazone formation depends upon the volume of the solvent used, dilute solutions favoring mono-thiosemicarbazone formation, whereas concentrated solutions favor the formation of bis-thiosemicarbazone. Likewise, treatment of **2a** with the mixed primary/secondary diamine, *N*-methylethylenediamine or *N*-methyl-1,3-diaminopropane, gave only the monosemicarbazone **4b** or **4c**. Further attempts to cyclodesulfurize the preformed thiosemicarbazones **4b** or **4c** in boiling toluene also failed.



4a, R = CH_3, R' = H, n = 2
b, R = R' = CH_3, n = 2
c, R = R' = CH_3, n = 3



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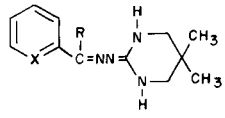
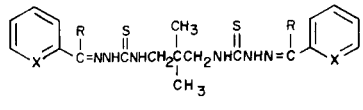
However, reaction of primary diamine, 2,2-dimethyl-1,3-diaminopropane, with **2a** yielded the corresponding unsymmetrical azine **6a** as the major, and the bis-thiosemicarbazone **7a** as the minor, product.



6a, X = N, R = CH_3
b, X = CH, R = H
c, X = CH, R = CH_3



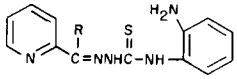
7a, X = N, R = CH_3
b X = CH, R = H
c, X = CH, R = CH_3

o-Phenylenediamine reacts in an analogous manner with **2a** to give monothiosemicarbazone, **8**, whereas *N,N'*-dimethyl-*o*-phenylenediamine gave azine, **9**, as the major product.

Table II

Condensation Products of **2b** and **2c** with Diamines

Compound No.	Diamine	Mp °C	Yield %	Recrystallization Solvent	^{1}H-NMR, δ (ppm)
3c	$CH_3NHCH_2CH_2NHCH_3$	71-73	62	cyclohexane	3.11 (br s, 4H), 3.28 (s, 6H), 7.28 (m, 3H), 7.59 (m, 2H), 8.13 (s, 1H)
3d	$CH_3NH(CH_2)_3NHCH_3$	79-80	41	cyclohexane	1.99 (m, 2H), 3.07 (s, 6H), 3.21 (t, 4H), 7.24-7.33 (m, 3H), 7.60-7.72 (m, 2H), 8.13 (s, 1H)
3e	$CH_3NHCH_2CH_2NHCH_3$	92-94	58	acetonitrile	2.38 (s, 3H), 3.12 (br s, 4H), 3.28 (s, 6H), 7.26-7.82 (m, 5H)
3f	$CH_3NH(CH_2)_3NHCH_3$	73-74	68	ethyl ether	1.90 (m, 2H), 2.38 (s, 3H), 3.08 (s, 6H), 3.21 (t, 4H), 7.25-7.43 (m, 3H), 7.75-7.86 (m, 2H)
6b	$(NH_2CH_2)_2C(CH_3)_2$	224-226	44	acetonitrile/chloroform	1.10 (s, 6H), 3.05 (d, 4H), 5.14 (br s, 1H), 6.45 (br s, 1H), 7.25-7.34 (m, 3H), 7.57-7.68 (m, 2H), 8.08 (s, 1H)
6c	$(NH_2CH_2)_2C(CH_3)_2$	138-139	20	ethyl ether	1.08 (s, 6H), 2.36 (s, 3H), 3.02 (d, 4H), 5.13 (br s, 1H), 6.42 (br s, 1H), 7.25 ~7.34 (m, 3H), 7.68 ~ 7.79 (m, 2H)



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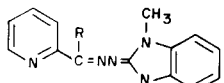

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Although related in structure to **2**, methyl aryldithiocarboxylates **10** and methyl *N*-aryldithiocarbamates (**11**) were reported to react with ethylenediamine in a different manner than **2** to give the cyclodesulfurization products, namely, 2-substituted 4,5-dihydroimidazoles and 2-arylaminoimidazoles, respectively [6,7].

The scope of the reaction was further probed using methyl 2-(phenylmethylene)hydrazinecarbodithioates **2b** and **2c** as starting materials. Overall, their treatment with *N,N'*-dimethylethylenediamine or *N,N'*-dimethyl-1,3-diaminopropane also gave good yield of the corresponding azines **3c-f** (*cf.* Table II). Likewise, treatment of **2b** or **2c**

Table III

Analytical Data for Condensation Products of **2a-c** with Diamines

Compound	Molecular Formula	Analysis % Calcd./Found C	H	N	S
3a	$C_{12}H_{17}N_5$	62.34	7.36	30.30	
		62.29	7.36	30.36	
3b	$C_{13}H_{19}N_5$	63.65	7.81	28.55	
		64.23	7.86	28.04	
3c	$C_{12}H_{16}N_4$	66.64	7.46	25.90	
		66.73	7.29	25.92	
3d	$C_{13}H_{18}N_4$	67.80	7.88	24.33	
		67.85	7.85	24.35	
3e	$C_{13}H_{18}N_4$	67.80	7.88	24.33	
		67.58	7.72	24.17	
3f	$C_{14}H_{20}N_4$	68.82	8.25	22.93	
		68.85	8.22	22.87	
4a	$C_{10}H_{15}N_5S$	50.61	6.37	29.51	13.51
		50.55	6.37	29.37	13.64
4b	$C_{11}H_{17}N_5S$	52.56	6.82	27.86	12.76
		52.66	6.72	27.72	12.80
4c	$C_{12}H_{19}N_5S$	54.31	7.22	26.39	12.08
		54.31	7.24	26.45	12.02
5	$C_{18}H_{22}N_8S_2$	52.15	5.35	27.03	15.47
		52.22	5.34	27.13	15.35
6a	$C_{13}H_{19}N_5$	63.65	7.81	28.55	
		63.72	7.71	28.53	
6b	$C_{13}H_{18}N_4$	67.80	7.88	24.33	
		67.88	7.78	24.30	
6c	$C_{14}H_{20}N_4$	68.82	8.25	22.93	
		68.42	8.30	22.43	
7a	$C_{21}H_{28}N_8S_2$	55.24	6.18	24.54	14.01
		55.25	6.17	24.58	13.94
7b	$C_{21}H_{26}N_6S_2$	59.12	6.14	19.70	15.03
		59.16	5.89	19.63	15.15
7c	$C_{23}H_{30}N_6S_2$	60.76	6.65	18.40	14.10
		60.50	6.69	18.27	13.57
8	$C_{14}H_{15}N_5S$	58.92	5.30	24.54	11.24
		59.01	5.33	24.86	11.06
9	$C_{16}H_{17}N_5$	68.79	6.13	25.07	
		68.92	6.26	24.83	

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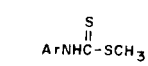

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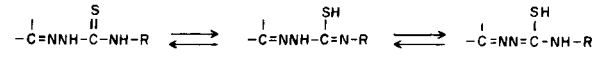
with 2,2-dimethyl-1,3-diaminopropane gave azine **6b** or **6c** and bis-thiosemicarbazones **7b** or **7c**, respectively. However, **2b** gave a better yield of the corresponding azine than **2c**, compound **7c** being the major product in the latter case.

The most likely mechanism for the formation of azine **3** from **2** involves the formation of an intermediate N^4,N^4-disubstituted thiosemicarbazone which undergoes internal nucleophilic addition of the terminal amino group to the thiocarbonyl function forming a tetrahedral thiol intermediate (Scheme 1). The latter subsequently loses a molecule of hydrogen sulfide to give azine **3**. In the case of N^4-monosubstituted thiosemicarbazones, tautomerization involving N^4-H (Scheme 2) is possible, reducing the electrophilicity of the thiocarbonyl carbon atom and, thus, diminishing the likelihood of the occurrence of cyclodesulfurization. Other reactions of thiosemicarbazones, such as the borohydride reduction of the azomethine bond [8] and a

Scheme 2



thiocarbonyl-activated transamination reaction [9], are reported to be influenced indirectly by the presence or absence of a proton on the terminal thiosemicarbazone nitrogen atom. Thus, only those diamines which will form an intermediate thiosemicarbazone in which N^4 lacks a proton yields the cyclodesulfurization product. However, one exception to this general observation is 2,2-dimethyl-1,3-diaminopropane which reacts with **2** to form cyclic product **6** in good yield with the formation of the corresponding bis-thiosemicarbazone **7** as a minor product. Although the formation of **6** involves the generation of intermediate thiosemicarbazone with a proton at N^4 position, the *gem*-dimethyl groups of 2,2-dimethyl-1,3-diaminopropane appear to exert favorable substituent effects on the thiosemicarbazone intermediate to facilitate the cyclization. Similar substituents effects that favor the formation of rings, such as epoxides, cyclic ethers, and anhydrides are disclosed in the literature [10-16].

This method described here provides a new and facile route for the synthesis of unsymmetrical heterocyclic azines by the treatment of methyl arylalkylidenehydrazinecarbodithioates with diamines *via* a cyclodesulfurization process.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Analyses were performed by Spang

Microanalytical Laboratory, Eagle Harbor, MI. Satisfactory microanalyses (±0.3%) were obtained for all compounds (Table III). Infrared spectra of solid samples were obtained as potassium bromide disks on a Perkin-Elmer Model 283 spectrophotometer. The nmr spectra were run on a JEOL FX90Q spectrometer using tetramethylsilane as an internal standard. Mass spectra were determined on a Finnigan 3100D spectrometer operated in the CI mode using methane as the reagent gas.

Methyl Phenylmethylenehydrazinecarbodithioate (**2b**).

Benzaldehyde (16 g, 0.15 mole) and methyl hydrazinecarbodithioate (20 g, 0.15 mole) [17] were dissolved in 200 ml of 95% ethanol containing 1 drop of concentrated hydrochloric acid. The solution was heated under reflux on a steam bath for 24 hours. After cooling, the crystals were collected, washed with cold ethanol and recrystallized from ethanol to give 23 g (73%) of pale yellow crystals of **2b**, mp 155-157°; nmr (deuteriochloroform): δ 2.67 (s, 3H, -SCH_3), 7.25-7.76 (m, 5H, Ar-H), 7.96 (s, 1H, -CH=N), 11.14 (s, 1H, NH).

Anal. Calcd. for $C_9H_{10}N_2S_2$: C, 51.40; H, 4.79; N, 13.31; S, 30.49. Found: C, 51.45; H, 4.78; N, 13.31; S, 30.42.

Methyl Phenylethylidenehydrazinecarbodithioate (**2c**).

The title compound was prepared by condensation of acetophenone (18 g, 0.15 mole) and methyl hydrazinecarbodithioate (20 g, 0.15 mole) according to the procedure given above to yield 30 g (89%) of **2c**, mp 143-145° (lit [18] mp 149-150.5°); nmr (deuteriochloroform): δ 2.29 (s, 3H, -CH_3), 2.65 (s, 3H, -SCH_3), 7.25-7.81 (m, 5H, Ar-H), 10.16 (s, 1H, -NH).

Anal. Calcd. for $C_{10}H_{12}N_2S_2$: C, 53.54; H, 5.39; N, 12.49; S, 28.58. Found: C, 53.56; H, 5.35; N, 12.45; S, 28.62.

Reaction of **2a** with Secondary Diamines. General Procedure.

Methyl 3-[1-(2-pyridinyl)ethylidene]hydrazinecarbodithioate (**2a**, 6.75 g, 0.03 mole) [17] and 0.03 mole of secondary diamine in 100 ml of 95% ethanol were heated under reflux for 12 hours causing the evolution of methanethiol and hydrogen sulfide. The solvent was evaporated to dryness under reduced pressure, and the solid residue was recrystallized from the appropriate solvent. When the product was an oil, purification was achieved by vacuum distillation. The physical properties of the products are listed on Table I.

Methyl phenylmethylenehydrazinecarbodithioate **2b** or methyl phenylethylidenehydrazinecarbodithioate **2c** were treated with appropriate diamines by the same procedure to give azines (Table II).

Reaction of **2a** with a Primary Diamine.

Carbodithioate **2a** (9 g, 0.04 mole) and ethylenediamine (2.4 g, 0.04 mole) in 150 ml of 95% ethanol were heated under reflux for 12 hours. The solvent was evaporated to dryness under the reduced pressure, and the residual oil solidified upon trituration with ethyl acetate. The solid was suspended in 200 ml of chloroform, the insoluble material was collected and recrystallized from dimethylformamide + methanol to give 3 g (36%) of white needles of *N,N'*-(1,2-ethylene)bis{2-[1-(2-pyridinyl)ethylidene]hydrazinecarbothioamide} (**5**), mp 219-221°.

The chloroform filtrate was evaporated to dryness and the residue was recrystallized from ethyl acetate to give 3.5 g (37%) of yellow needles of *N*-(2-aminoethyl)-2-[1-(2-pyridinyl)ethylidene]hydrazinecarbothioamide (**4a**), mp 128-129°.

When the identical reaction was carried out in 90 ml of 95% ethanol, it gave 57% of **5** and 14% of **4a**.

Reaction of **2a** with 2,2-Dimethyl-1,3-diaminopropane.

Carbodithioate **2a** (9 g, 0.04 mole) and 2,2-dimethyl-1,3-diaminopropane (4 g, 0.04 mole) in 150 ml of 95% ethanol were heated on a steam bath for 12 hours. The solvent was evaporated to dryness under the reduced pressure and the oily residue crystallized upon trituration with small amount of ethanol. The crude product was recrystallized from acetonitrile to give 5 g (45%) of azine **6a** as pale yellow crystals, mp 183-185°. The mother liquid was concentrated to give crude bis-thiosemicarbazone **7a** which was crystallized from acetonitrile to give 0.7 g (8%) of **7a**, mp 194-196°.

Carbodithioate **2b** (3.1 g, 0.015 mole) was treated with 2,2-dimethyl-1,3-diaminopropane (1.53 g, 0.015 mole) under the identical conditions to give 1.5 g (44%) of azine **6b**, mp 224-226° (acetonitrile) and 0.4 g of bis-thiosemicarbazone **7b**, mp 238-239° (ethanol/chloroform).

Treatment of **2c** with 2,2-dimethyl-1,3-diaminopropane by the same procedure gave compound **6c** (19%), mp 138-139° (ethyl ether) and **7c** (60%), mp 203-205° (ethanol).

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