Acknowledgment. We are pleased to acknowledge support for this work by the National Science Foundation (NSF CHE-8614665 and CHE-9020793).

Supplementary Material Available: ^1H and ^{13}C NMR spectra for **6c**, **6d**, **7c**, **7d**, **14a**, **17**, **18a**, **18b**, **22**, and the phosphine oxide of **25** (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

The Reactions of 5-Amino-1,2,3,4-thiatriazoles with Isocyanates

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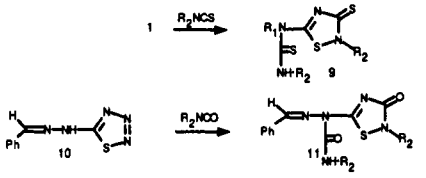
The reaction of 5-(arylamino)-1,2,3,4-thiatriazoles **1** with isocyanates initially gives 1,2,3,4-thiatriazol-5-ylureas **3** which can be isolated when the aryl group has *o*-alkyl substituents. Compounds **3** rearrange to **21** in the presence of triethylamine and then react with the second equivalent of isocyanate to give (4-aryl-2-alkyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene)ureas **12** rather than the (3-oxo-Δ^4-1,2,4-thiadiazolin-5-yl)ureas **7** which had been proposed previously.[1] The latter compounds, prepared from **8** and isocyanates, also rearrange to **12**. Mechanisms incorporating these observations are proposed (Schemes IV and VI). The structure of **12** was confirmed by single-crystal X-ray analysis of [4-(2,6-dimethylphenyl)-2-methyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene]methylurea **12baa**.

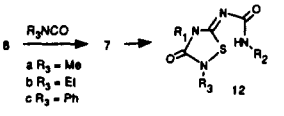
Introduction

Several years ago we reported the reaction of 5-(arylamino)-1,2,3,4-thiatriazoles **1** with isocyanates.[1] At that time the products were postulated to be (3-oxo-Δ^4-1,2,4-thiadiazolin-5-yl)ureas **7** based on ^1H and ^{13}C NMR and IR spectra, elemental analyses, and an alternate synthetic route to the same products. The proposed reaction sequences were as shown in Scheme I.

Recently the reactions of **1** with alkyl isothiocyanates were postulated to give **9**[2] and the 5-(benzylidinehydrazino)-1,2,3,4-thiatriazole **10** with isocyanates to give **11**[3] by analogy with our earlier work.



Subsequent work in our laboratory has revealed that the original[1] structure assignment as **7** was not correct due to a common pitfall in multiheteroatom cyclic systems: the unexpected and unrecognized rearrangements which occurred both during the reaction of **1** with isocyanates and also during the last step of the alternate synthesis, namely the reaction of **8** with the isocyanate. The latter reaction did not stop at **7**, but continued on to **12**. A recent review of rearrangements pertinent to this heterocyclic system has been published.[4] The present work not only establishes the correct structure as **12**, but also reveals some of the details of the reaction sequence. For compounds **3**, **7**, **8**, and **12** the letters following the number of a structure refer to R_1, R_2, and R_3 in that order.

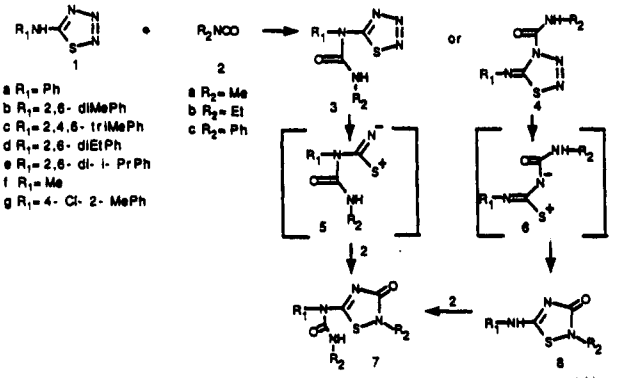


Results and Discussion

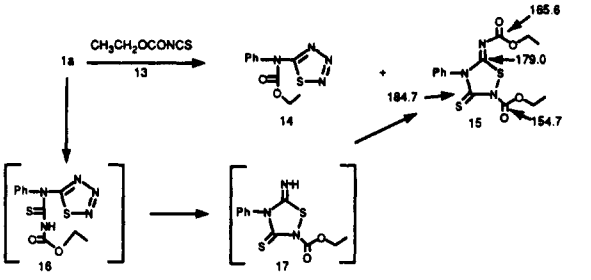
1. Reaction with Ethoxycarbonyl Isothiocyanate. The initial indication with the originally proposed structure required a revision came from the reaction of **1a** with ethoxycarbonyl isothiocyanate (**13**), which we expected to give **9** (R_1 = Ph, R_2 = $CO_2CH_2CH_3$). Instead, we obtained two products (Scheme II), whose structures were eventually determined to be **14** and **15**. The structure of **14** was proven by its synthesis from **1a** and ethyl chloroformate and by the ^{13}C NMR (C=O at δ 152.1 and C-5 at δ 170.7 as would be expected for carbamates[5] and acylated thiatriazoles[6]).

Since we had previously found that an NH was necessary in the 5-position for reactions with isocyanates,[1] we knew that **14** was not an intermediate because it was not capable of further reaction. The formation of **15** then had

Scheme I



Scheme II



(1) Kaugars, G.; Rizzo, V. L. *J. Org. Chem.* **1979**, *44*, 3840.
(2) Graubaum, H. *J. Prakt. Chem.* **1989**, *331*, 115.
(3) Graubaum, H.; Seeboth, H. *J. Prakt. Chem.* **1987**, *329*, 409.
(4) L'abbé, G. *J. Heterocycl. Chem.* **1984**, *21*, 627.
(5) Levy, G. C.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*; Wiley-Interscience: New York, 1972; p 126.
(6) L'abbé, G.; Toppet, S.; Willcox, A.; Mathys, G. *J. Heterocycl. Chem.* **1977**, *14*, 1417.

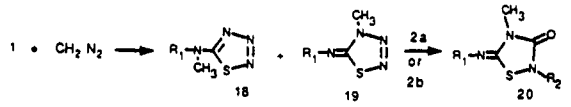
0022-3263/92/1957-1671$03.00/0

Table I. Reactions of 1 with Diazomethane

substrate	18/19 (as 20) ratio
1a	1:1.06[a]
1b	1:1.32[b]
1d	1:1.90
1e	1:2.42

[a] See ref 8. [b] A ratio of 1:1.46 was obtained with ethyl isocyanate (2b).

Scheme III



to be from the alternative course: initial addition to the isothiocyanate. Elemental analysis of 15 showed that it was missing HNCS from the product expected from the addition of 2 equiv of 13. We also observed that a full equivalent of base (usually triethylamine) was required for this reaction to go to completion and that the rate of gas evolution was closely coupled to the rate of triethylamine addition. Therefore 15 had to be formed by loss of HNCS during the reaction with the second equivalent of the isothiocyanate. Therefore we propose that the reaction initially gives 16, which rearranges to 17 with loss of nitrogen. The intermediate 17, which contains the ring system of the product, then reacts with 13 by nucleophilic displacement of NCS. The end product from this sequence was identified as 15 by comparison of spectral data, especially the ^{13}C NMR, with similar model compounds.[7] This conclusion set the stage for a reexamination of our earlier[1] work.

2. Isolation of Intermediates. One of the originally postulated intermediates (3) derives from the reaction of isocyanate on the 5-amino group, the other (4) from reaction on the 4-nitrogen. We had briefly investigated the reactions of 1 with diazomethane and had found that the selectivity of alkylation was influenced by steric hindrance: bulky alkyl groups in the 2- and 6-positions of the phenyl ring increased N-4 alkylation and decreased 5-amino alkylation. The results are summarized in Table I. In earlier work L'Abbe et al.[8] found that 1a gave a 1:1.06 ratio of 18a:19a. In our work the 5-methylamino compounds (18) were isolated as such, but the 4-methyl (19) was reacted in situ with methyl isocyanate as described by L'Abbe et al.[9,10] to give 20 (Scheme III). The latter reaction, as judged by TLC analysis, appeared to be essentially quantitative as had been found for the reaction of 1a with *n*-butyl isocyanate.[9]

Since the alkylation reaction of 1 was obviously affected by steric factors, we reasoned that the reaction with isocyanates would also be affected. This was indeed the case, although the result was somewhat surprising. We had expected that steric hindrance would produce an effect

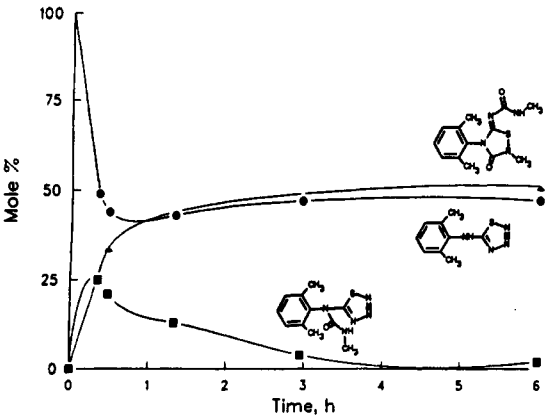


Figure 1. Reaction of 1b (0.5 M) with an equimolar amount of 2a in $CDCl_3$. Relative concentrations of 1b (●), 3ba (■), and 12baa (△).

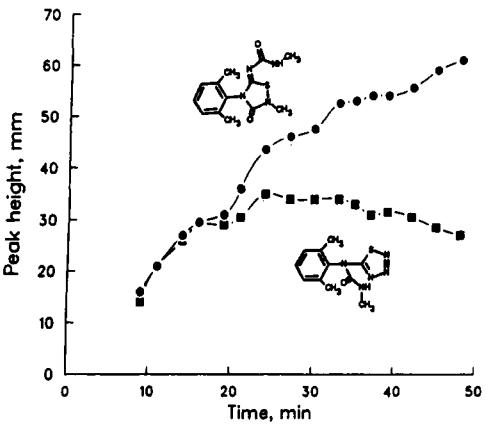


Figure 2. Reaction of 1b (0.5 M) with an equimolar amount of 2a in $CDCl_3$. Relative concentrations of 3ba (■) and 12baa (●).

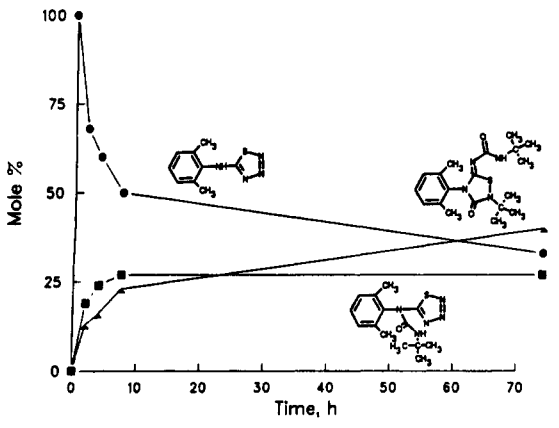
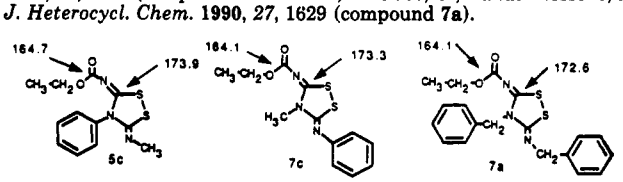


Figure 3. Reaction of 1b (0.5 M) with an equimolar amount of *tert*-butyl isocyanate in $CDCl_3$. Relative concentrations of 1b (●), 3bd (■), and 12bdd (△).

analogous to that observed with the methylation reaction: partial reaction on N-4. TLC analysis showed that in several cases (1b,c,e) two products were formed, but that the product with the higher R_f disappeared as the reaction proceeded to form 12. Careful monitoring of the course of the reaction by TLC allowed us to quench the reaction so as to maximize the amount of the intermediate, which was isolated in two cases. The two isolated compounds turned out to be intermediates 3ca and 3ea, which were characterized by elemental analysis and ^1H and ^{13}C NMR spectral data. The ^{13}C data unequivocally identify 3 as the structure of the intermediate and rule out 4 on the basis of the aryl shifts, particularly the ipso carbon, which in 4 would be shifted downfield to about δ 150.[1,11] Inter-

(7) L'abbé, G.; Timmerman, A.; Martens, C.; Toppet, S. *J. Org. Chem.* **1978**, *43*, 4951 (compounds 5c and 7c). L'abbé, G.; Vandenriessche, A. *J. Heterocycl. Chem.* **1990**, *27*, 1629 (compound 7a).



(8) L'abbé, G.; Verhelst, G.; Toppet, S. *J. Org. Chem.* **1977**, *42*, 1159. The ratio is of 18a:19a.

(9) L'abbé, G.; Verhelst, G. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 489.

(10) L'abbé, G.; Weyns, N.; Sannen, I.; Delbeke, P.; Toppet, S. *J. Heterocycl. Chem.* **1991**, *28*, 405.

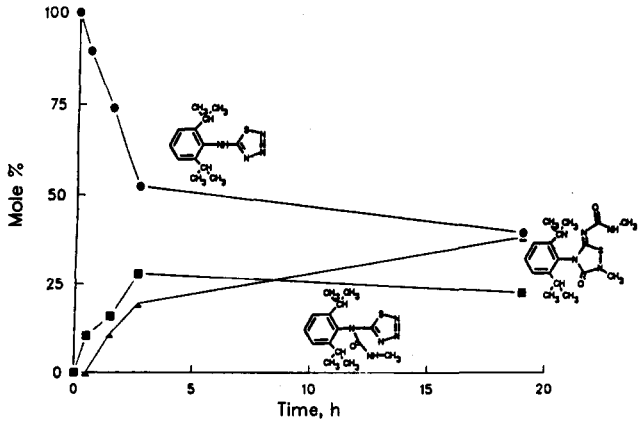
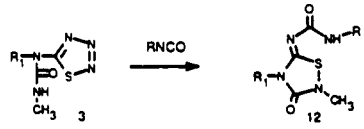


Figure 4. Reaction of **1e** (0.5 M) with an equimolar amount of **2a** in $CDCl_3$. Relative concentrations of **1e** (●), **3ea** (■), and **12eaa** (▲).

estingly, the 2,6-diisopropylphenyl group is so hindered that the isopropyl groups are clean doublets both in the ^1H and ^{13}C NMR in the starting **1** and all products. Kinetic studies by ^1H NMR showed that the intermediates reached a maximum concentration and then decreased as the reaction proceeded to form **12** (Figures 1–4). The reaction of **1b** with **2a** was followed by integration of the aryl-CH_3 singlets (δ 2.28 for **1b**, δ 2.05 for **3ba**, and δ 2.10 for **12baa**) or by peak height (Figure 2). The reaction of **1e** with **2a** was followed by integration of the NCH_3 doublets (δ 2.88 for **3ea** and δ 2.78 for **12eaa**) and one of the peaks of the δ 3.20 pentuplet for **1e**. The figures show that **3** is formed very rapidly in all cases, but when substantial steric hindrance in either the isocyanate (Figure 3) or the thiatriazole (Figure 4) is present, then **3** persists for an extended period.

In the cases where the intermediate was isolated the reaction was followed by TLC in hexane/EtOAc systems (1:1 or 2:1) in which **1** had an R_f of ca. 0.9, **3** ca. 0.6, and **12** ca. 0.5 or by ^1H NMR to determine the approximate optimal isolation time since the rate was dependent on the catalyst concentration. It was surprising to find that we were able to isolate **3** since steric hindrance should slow down the initial reaction with isocyanate on the 5-amino group. Our inability to detect this intermediate in previous work suggested that the reaction with the second equivalent of isocyanate was the faster step, but obviously such is not the case with the hindered intermediates.

3. Reactions of Intermediates. (a) The two isolated intermediates **3ca** and **3ea** could be further reacted with isocyanates in the presence of Et_3N to form compounds of the type **12**. Reaction of **3ca** or **3ea** with **2a** gave the



same compound as from **1c** or **1e** and **2a**. Compound **3ea** reacted with ethyl isocyanate to give a product with a singlet for the NCH_3 and a pentuplet for $NHCH_2CH_3$ in the ^1H NMR spectrum. This confirmed the revised structure as **12**, rather than **7**, since the isocyanate that reacts with the 5-amino in the first step is the one that is incorporated into the ring.

(b) The intermediate **3ea** in the presence of Et_3N rearranged to another intermediate which could not be isolated pure due to appreciable decomposition during silica

(11) L'abbé, G.; Verhelst, G.; Huybrechts, L.; Toppet, S. *J. Heterocycl. Chem.* **1977**, *14*, 515.

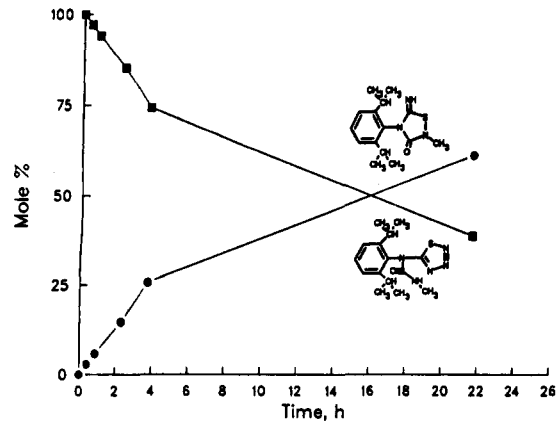


Figure 5. Rearrangement of **3ea** to **21ea** in $CDCl_3$ with Et_3N catalysis. Relative concentrations of **3ea** (■) and **21ea** (●).

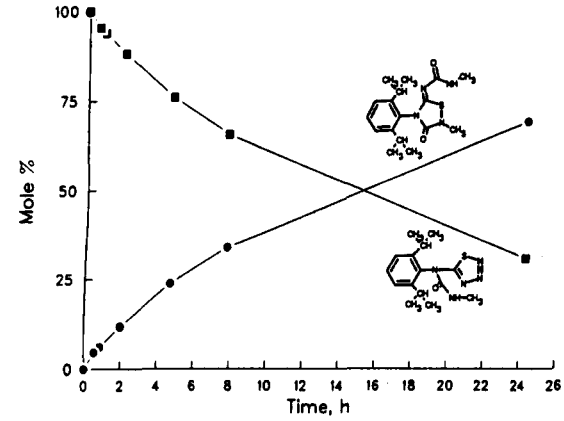
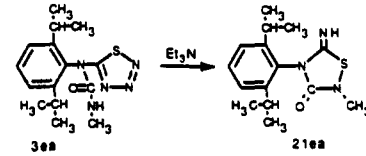


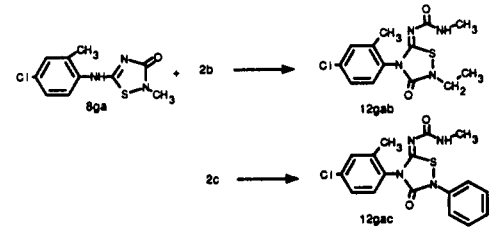
Figure 6. Reaction of **3ea** with methyl isocyanate in $CDCl_3$ with Et_3N catalysis. Relative concentrations of **3ea** (■) and **12eaa** (●).

gel chromatography. However, it could be characterized as **21ea** on the basis of ^1H and ^{13}C NMR spectra in a mixture of **3ea** and **21ea**. Thus the NCH_3 was found at δ 3.20 (singlet) and at δ 31.75, respectively, both of which are characteristic of the ring NCH_3.

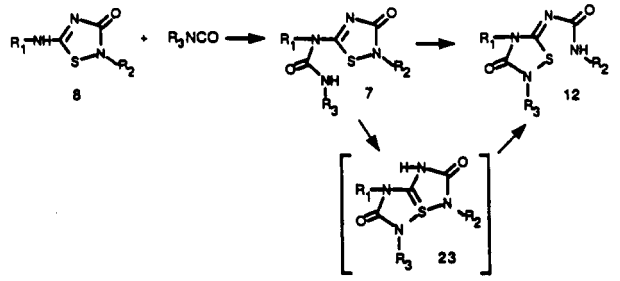


As shown in Figures 5 and 6, the rearrangement with Et_3N and the reaction with methyl isocyanate under the identical conditions proceed at the same rate. Therefore the rate-determining step for this intermediate sequence is the rearrangement of **3** to **21**. These reactions were followed by integration of the δ 2.92 NCH_3 doublet of **3ea**, the δ 3.20 NCH_3 singlet of **21ea**, and the δ 3.17 singlet NCH_3 of **12eaa**.

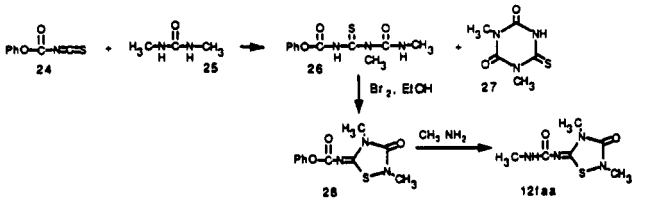
4. Rearrangement of Thiadiazole 8 upon Reaction with Isocyanates and Isothiocyanates. In our earlier work[1] **8aa** and **8ga** were synthesized by an alternate route and then were reacted with **2a** to give the same products, respectively, as from **1a** and **1g** with 2 equiv of **2a**.



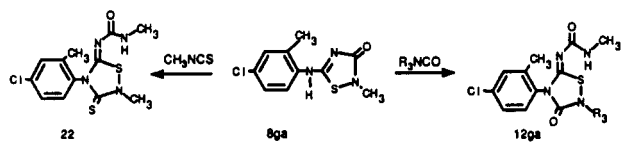
Scheme IV



Scheme V



However, reaction of **8ga** with a different isocyanate **2b** showed that the 2-*N*-alkyl of 8 was now in the side chain, but that the second isocyanate was incorporated into the ring. This sequence of events could be deduced from the ^{1}H NMR. Thus the NCH_3 became a doublet and the methylene group from the ethyl isocyanate in **12gab** was a sharp quartet. In contrast, reaction of **1a** and **1e** with **2b** gave compounds **12abb** and **12ebb** whose ^{1}H NMR clearly showed pentuplets for the methylene groups from the ethyl isocyanate. The described sequence of events was also demonstrated by the reaction of **8ga** with **2c** to give **12gac** in which the NCH_3 was a doublet. In addition, **8ga** reacted readily with methyl isothiocyanate to give **22**,

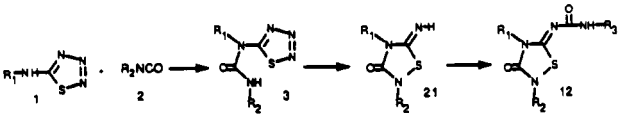


whose ^{13}C NMR spectrum showed the thiourea at δ 172.6, but lacked the ring C=O at ca. δ 154. Thus it became obvious that our original alternate synthesis had led us astray, because **7** is only an intermediate which undergoes a rearrangement according to the Boulton-Katritzky scheme[12] or, more generally, according to the "three side-chain atom" rearrangement,[4] a variant of which is via a thiapentalene type intermediate **23**.[4,13] These possibilities are shown in Scheme IV.

5. Alternate Synthesis of 12faa. Compound **12faa**, which was described in our earlier publication as **7faa**,[1] was also prepared by the route shown in Scheme V. The reaction of 1,3-dimethylurea (**25**) with phenoxycarbonyl isothiocyanate (**24**) gave **26**. This compound cyclized to **27** upon recrystallization or even standing at ambient temperature for several days, and therefore it was used immediately to oxidatively cyclize[14] to **28**, which reacted readily with methylamine to give **12faa**. This was identical to the compound obtained by the reaction of **1f** and **2a**.

6. Crystal Structure. Confirmation of the structure of **12** was obtained by a single-crystal X-ray analysis of **12baa** (see the supplementary material). The notable features of **12baa** are the short S···O distance (2.30 Å) and the long N—S (1.73 Å) and C=O (1.25 Å) bonds which

Scheme VI



indicate an appreciable bonding interaction between the O and S. These features are quite similar to those found in 5-imino-Δ^3-1,2,4-thiadiazolines.[15]

Conclusion

The identification of the intermediates **3** and **21** defines the sequence shown in Scheme VI. When R_1 or R_2 is bulky, the rearrangement of **3** to **21** is slowed sufficiently to allow isolation of **3** since the rearrangement requires coplanarity of the thiatriazole ring and the side-chain urea.

Since the reaction of **8** with isocyanates leads to **12** as well, the reasonable sequence appears to be the one shown in Scheme IV: reaction on the NH followed by a rearrangement which could be of the same type as for **3** to **21**.

Experimental Section

Compounds **1a**, **1f**, and **1g** were prepared as reported.[1]

5-Amino-1,2,3,4-thiatriazoles (1) were prepared by the previously described procedure[1] from the thiosemicarbazides, which were prepared from the known[16,17] thioureas. Since the compounds tend to decompose appreciably at elevated temperatures, they were purified at fairly low temperatures as described for each one.

***N*-(2,6-Dimethylphenyl)-1,2,3,4-thiatriazol-5-amine (1b)**: purified by dissolving in boiling ether, filtering, then cooling to −15 °C; mp 107.5 °C; ^{1}H NMR δ 2.32 (s, 6 H), 7.14 (s, 3 H), 10.33 (bs, 1 H); IR 3180, 1600, 1540 cm^{-1}. Anal. Calcd for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16; S, 15.54. Found: C, 52.11; H, 4.99; N, 27.57; S, 15.51.

***N*-(2,4,6-Trimethylphenyl)-1,2,3,4-thiatriazol-5-amine (1c)**: purified by dissolving in EtOAc at 45 °C, filtering, then cooling to −10 °C; mp 113.9 °C; ^{1}H NMR δ 2.30 (bs, 9 H), 7.01 (bs, 2 H), 10.33 (bs, 1 H); ^{13}C NMR δ 179.4, 136.6, 133.9, 132.8, 127.8, 18.8, 15.6; IR 3160, 3120, 1610, 1545 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43; S, 14.55. Found: C, 54.24; H, 5.61; N, 25.31; S, 14.60.

***N*-(2,6-Diethylphenyl)-1,2,3,4-thiatriazol-5-amine (1d)**: purified the same as **1c**; mp 99.5–101.5 °C; ^{13}C NMR δ 180.0, 139.3, 135.3, 127.4, 125.7, 22.5, 12.8; IR 3160, 1550 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_4S$: C, 56.38; H, 6.02; N, 23.91; S, 13.69. Found: C, 56.19; H, 5.99; N, 24.43; S, 13.67.

***N*-[2,6-Bis(1-methylethyl)phenyl]-1,2,3,4-thiatriazol-5-amine (1e)**: mp 116.1 °C; ^{1}H NMR δ 1.20 (d, 12 H), 3.20 (p, 2 H), 7.3 (m, 3 H); ^{13}C NMR δ 182.7, 146.2, 135.8, 130.1, 124.9, 28.7, 24.8, 23.0; IR 3160, 1555 cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_4S$: C, 59.51; H, 6.91; N, 21.36; S, 12.22. Found: C, 59.46; H, 6.84; N, 21.54; S, 12.22.

***N'*-Methyl-*N*-1,2,3,4-thiatriazol-5-yl-*N*-(2,4,6-trimethylphenyl)urea (3ca) and [4-(2,4,6-Trimethylphenyl)-2-methyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene]methylurea (12caa)**. A solution of **1a** (4.41 g, 20.0 mmol), **2a** (3.00 mL, 50.9 mmol), and Et_3N (10 drops) in 40 mL of THF was stirred at ambient temperature for 19 h. The reaction was followed by TLC in 1:1 and 2:1 hexanes/EtOAc. The solvent was removed, and the residue was triturated with 75 mL of EtOAc. The solids were filtered to give **12caa** (4.30 g, 70%). The filtrate was evaporated to give **3ca** (1.89 g, 34%) slightly contaminated by **12caa** (TLC

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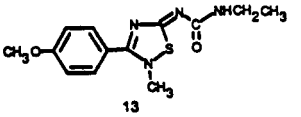
(15) L'abbé, G.; Vermeulen, G.; Toppet, S.; King, G. S. D.; Aerts, J.; Sergier, L. *J. Heterocycl. Chem.* **1981**, *18*, 1309. The S···O distance in **13** is 2.29 Å, the N—S is 1.74 Å, and C=O is 1.26 Å.



13

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in 2:1 and 1:1 hexane/EtOAc). The analytical sample of **12caa**, mp 234.9 °C, was obtained by recrystallization from EtOAc: ^{1}H NMR δ 2.07 (s, 6 H), 2.28 (s, 3 H), 2.73 (d, 3 H), 3.15 (s, 3 H), 5.6 (b, 1 H), 6.95 (bs, 2 H); IR 3320, 1700, 1605 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_4O_2S$: C, 54.88; H, 5.92; N, 18.27; S, 10.47. Found: C, 54.85; H, 5.75; N, 18.03; S, 10.34. The analytical sample of **3ca**, mp 137–8 °C dec, was obtained by dissolving in EtOAc, adding hexane until cloudy, filtering, evaporating the filtrate, and triturating the residue with ether: ^{1}H NMR δ 2.03 (s, 6 H), 2.35 (s, 3 H), 2.92 (d, 3 H), 5.5 (b, 1 H), 7.07 (bs, 2 H); ^{13}C NMR δ 165.6, 152.0, 139.4, 135.8, 130.8, 129.3, 30.4, 27.2, 21.2, 17.6; IR 3340, 1690, 1610 cm^{-1}. Anal. Calcd for $C_{12}H_{15}N_5OS$: C, 51.97; H, 5.45; N, 25.25; S, 11.56. Found: C, 52.34; H, 5.67; N, 24.00; S, 11.67. A solution of **3ca** (69 mg, 0.25 mmol) in 0.50 mL of THF was treated with **2a** (0.10 mL, 1.7 mmol) and Et_3N (3 drops) and held at ambient temperature for 16 h. TLC in hexane/EtOAc systems shows only **12caa**.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-methyl-*N*-1,2,3,4-thiatriazolyl-5-ylurea (3ea).** A solution of **1e** (1.31 g, 5.00 mmol) in 10 mL of $CDCl_3$ containing 0.5% TMS was treated with **2a** (0.45 mL, 7.5 mmol) and three drops of Et_3N. The reaction was followed by ^{1}H NMR to detect the amount of monoadduct. After 3 h at ambient temperature the solvent was removed on a rotary evaporator, and the residue was dissolved in 5 mL of 9:1 toluene/EtOAc and 1 mL of $CHCl_3$ and chromatographed on a size C Merck prepacked silica gel column with 9:1 toluene/EtOAc to yield **3ea** (0.39 g, 24%): mp 120.2 °C dec; ^{1}H NMR δ 1.06 (d, 6 H), 1.17 (d, 6 H), 2.61 (p, 2 H), 2.92 (d, 3 H), 5.09 (q, 1 H), 7.38 (d, 2 H), 7.56 (t, 1 H); ^{13}C NMR δ 170.8, 154.7, 146.8, 131.5, 131.0, 125.7, 28.7, 27.9, 24.0, 23.9; IR 3360, 1685 cm^{-1}. Anal. Calcd for $C_{15}H_{21}N_5OS$: C, 56.40; H, 6.63; N, 21.92; S, 10.04. Found: C, 56.68; H, 6.74; N, 21.97; S, 10.03.

Ethyl(2-ethyl-3-oxo-4-phenyl-1,2,4-thiadiazolidin-5-ylidene)urea (12abb). A solution of **1a** (8.91 g, 50.0 mmol), **2b** (10.0 mL, 0.126 mol), and Et_3N (0.5 mL) in 100 mL of THF was stirred at ambient temperature for 70 h and poured onto ice, and the solids were washed with water, dried, and then recrystallized from a mixture of cyclohexane and EtOH to yield **12abb** (11.83 g, 81%): mp 143.8 °C; ^{1}H NMR δ 1.09 (t, 3 H), 1.30 (t, 3 H), 3.22 (p, 2 H), 3.63 (q, 2 H), 5.53 (t, 1 H), 7.2–7.6 (m, 5 H); ^{13}C NMR (DMSO-d_6) δ 165.8, 164.1, 151.5, 135.5, 129.1, 128.8, 128.5, 38.4, 34.8, 14.6, 13.9; IR 3320, 1710, 1612 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_4O_2S$: C, 53.41; H, 5.52; N, 19.16; S, 10.97. Found: C, 53.36; H, 5.56; N, 19.51; S, 10.86.

[4-(2,6-Dimethylphenyl)-2-methyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene]methylurea (12baa). The procedure described for **12abb** was used with **1b** (10 mmol) and **2a** (25 mmol). The product was recrystallized from hexanes/EtOAc to yield **12baa** (0.92 g, 31%): mp 192.6 °C; ^{1}H NMR δ 2.10 (s, 6 H), 2.75 (d, 3 H), 3.15 (s, 3 H), 5.47 (b, 1 H), 7.0–7.3 (m, 3 H); ^{13}C NMR δ 165.5, 151.9, 136.2, 133.4, 129.6, 128.5, 30.3, 27.2, 17.7; IR 3350, 1710, 1610 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_4O_2S$: C, 53.41; H, 5.52; N, 19.16; S, 10.97. Found: C, 53.52; H, 5.52; N, 19.44; S, 11.24.

[4-[2,6-Bis(1-methylethyl)phenyl]-2-methyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene]methylurea (12eaa). The procedure described for **12abb** was used on a 10-mmol scale of **1e** and 27 mmol of **2a**. Characterization of **12eaa**: mp 247.5 °C; ^{1}H NMR δ 1.15 (d) and 1.19 (d) (12 H), 2.62 (p, 2 H), 2.78 (d, 3 H), 3.17 (s, 3 H), 5.56 (q, 1 H), 7.27 (d, 2 H), 7.45 (t, 1 H); ^{13}C NMR δ 166.4, 165.5, 152.6, 146.5, 130.7, 130.3, 124.1, 30.4, 29.0, 27.2, 23.9, 23.9; IR 3305, 1705, 1620 cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_4O_2S$: C, 58.60; H, 6.94; N, 16.08; S, 9.20. Found: C, 58.77; H, 6.97; N, 16.01; S, 9.34.

[4-[2,6-Bis(1-methylethyl)phenyl]-2-methyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene]ethylurea (12eba). A solution of **3ea** (192 mg, 0.60 mmol), **2b** (70 μL, 0.88 mmol), and Et_3N (1 drop) in 2 mL of THF was allowed to stand at ambient temperature for 4 d. The solvent was evaporated, and the residue was recrystallized from EtOH (6 mL) to yield **12eba** (154 mg, 71%): mp 231.7 °C; ^{1}H NMR δ 0.98–1.24 (2 d and t, 15 H), 2.64 (p, 2 H), 3.15 (s, 3 H), 3.22 (q, 2 H), 5.40 (bt, 1 H), 7.1–7.5 (m, 3 H); IR 3280, 1705, 1625 (sh), 1610 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_4O_2S$: C, 59.64; H, 7.23; N, 15.46; S, 8.85. Found: C, 59.33; H, 7.30: N, 15.35; S, 8.83.

[4-[2,6-Bis(1-methylethyl)phenyl]-2-ethyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene]ethylurea (12ebb). The procedure described for **12abb** was used with **1e** (15 mmol) and **2b** (40 mmol). The product was recrystallized from cyclohexane to yield **12ebb** (3.71 g, 66%): mp 197.3 °C; ^{1}H NMR δ 1.07 (t), 1.10 (d), 1.20 (d), and 1.30 (t) (18 H), 2.67 (p, 2 H), 3.25 (p, 2 H), 3.67 (q, 2 H), 5.40 (t, 1 H), 7.1–7.5 (m, 3 H); IR 3280, 1705, 1625 (sh), 1610 cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_4O_2S$: C, 60.61; H, 7.50; N, 14.88; S, 8.52. Found: C, 60.44; H, 7.48; N, 14.85; S, 8.68.

[4-(4-Chloro-2-methylphenyl)-2-ethyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene]methylurea (12gab). A suspension of **8ga**[1] (5.11 g, 20.0 mmol) and **2b** (2.50 mL, 31.6 mmol) in 50 mL of THF was stirred at ambient temperature overnight (a solution was obtained in 15 min) and then worked up as described for **12baa**. Recrystallization from MeOH gave **12gab** (4.53 g, 69%): mp 154.5 °C; ^{1}H NMR δ 1.30 (t, 3 H), 2.12 (s, 3 H), 2.74 (d, 3 H), 3.60 (q, 2 H), 5.54 (q, 1 H), 7.0–7.35 (m, 3 H); ^{13}C NMR δ 165.9, 165.2, 151.4, 138.2, 135.3, 132.7, 131.1, 129.8, 127.2, 39.2, 27.2, 17.6, 14.1; IR 3320, 1705, 1615 cm^{-1}. Anal. Calcd for $C_{13}H_{15}ClN_4O_2S$: C, 47.48; H, 4.63; Cl, 10.85; N, 17.14; S, 9.81. Found: C, 47.62; H, 4.61; Cl, 10.96; N, 17.23; S, 10.03.

[4-(4-Chloro-2-methylphenyl)-3-oxo-2-phenyl-1,2,4-thiadiazolidin-5-ylidene]methylurea (12gac). The procedure described for **12gab** was used with 10 mmol of **8ga** and 13.4 mmol of **2c**. Chromatography on silica gel with 3:1 hexanes/EtOAc gave **12gac** (3.33 g, 89%). Recrystallization from MeOH gave the analytical sample: mp 165.0 °C; ^{1}H NMR δ 2.17 (s, 3 H), 2.75 (d, 3 H), 5.60 (q, 1 H), 7.0–7.7 (m, 8 H); ^{13}C NMR δ 165.8, 165.5, 150.6, 138.2, 136.5, 135.5, 132.5, 131.2, 129.8, 129.4, 127.3, 126.4, 122.8, 27.3, 17.7; IR 3410, 1702, 1615 cm^{-1}. Anal. Calcd for $C_{17}H_{15}ClN_4O_2S$: C, 54.47; H, 4.03; Cl, 9.46; N, 14.95; S, 8.55. Found: C, 54.32; H, 4.07; Cl, 9.55; N, 14.97; S, 8.47.

***N*-Phenyl-1,2,3,4-thiatriazole-5-carbamic Acid Ethyl Ester (14).** The thiatriazole **1a** (5.35 g, 30.0 mmol) in 50 mL of THF was treated with Et_3N (5.0 mL, 36 mmol) and then with ethyl chloroformate (3.25 g, 30.0 mmol) at 17–30 °C. The resulting mixture was stirred for 30 min and poured into water, and the precipitate was collected, washed with water, and dried to yield 6.90 g of material, which was recrystallized from cyclohexane/benzene to yield **14** (5.62 g, 75%): mp 114.0 °C; ^{1}H NMR δ 1.23 (t, 3 H), 4.37 (q, 2 H), 7.15–7.65 (m, 5 H); ^{13}C NMR δ 170.7, 152.1, 135.0, 127.6, 127.3, 125.6, 63.4, 11.9; IR 1715, 1590 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_4O_2S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 48.36; H, 3.96; N, 22.42.

5-[(Ethoxycarbonyl)imino]-4-phenyl-3-thioxo-1,2,4-thiadiazolidene-2-carboxylic Acid Ethyl Ester (15). The thiatriazole **1a** (7.13 g, 40.0 mmol) in 100 mL of THF was treated with **13** (10.50 g, 80.0 mmol) and then with Et_3N (6.00 mL, 43.2 mmol) dropwise at 18–24 °C. The temperature was maintained with an ice bath. The reaction mixture was stirred at rt for 67 h, and the solid **15** (3.83 g, 27%) were filtered. The filtrate was evaporated to dryness, and the residue was chromatographed on four size C Merck prepacked silica gel columns with 1.5 L of 25% EtOAc in hexanes, then with 28% EtOAc in hexanes to yield **14** (0.49 g, 5%) whose IR spectrum and TLC behavior was identical to the material prepared above, and then a mixture of **14** and **1a** (1.40 g), pure **1a** (1.07 g, 15%), and **15** (5.17 g, 37%). The analytical sample of **15**, mp 172.1 °C, was obtained by recrystallization from EtOAc; ^{1}H NMR δ 1.20 and 1.27 (2 t, 6 H), 4.22 and 4.33 (2 q, 4 H), 7.1–7.6 (m, 5 H); ^{13}C NMR δ 184.7 (s), 179.0 (s), 165.6 (t, J = 3.0), 154.7 (t, J = 3.4), 138.6, 129.5, 129.2, 127.7, 65.1, 62.3, 14.3, 14.0; IR 1710, 1645 cm^{-1}. Anal. Calcd for $C_{14}H_{15}N_3O_4S_2$: C, 47.58; H, 4.28; N, 11.89; S, 18.14. Found: C, 47.66; H, 4.30; N, 12.11; S, 18.13.

***N*-(2,6-Dimethylphenyl)-*N*-methyl-1,2,3,4-thiatriazol-5-amine (18b) and 5-[(2,6-Dimethylphenyl)imino]-2,4-dimethyl-1,2,4-thiadiazolidin-3-one (20ba).** A suspension of **1b** (2.06 g, 10.0 mmol) in 50 mL of ether was treated with a diazomethane solution generated from 50 mmol of Diazald. After 3 h the solution was purged with N_2, dried over $MgSO_4$, and treated with **2a** (0.59 mL, 10.0 mmol). The solution was stirred overnight at ambient temperature and evaporated to dryness, and the residue was chromatographed on two size C Merck prepacked silica gel columns with 5:1 hexane/EtOAc to yield **18b** (0.93 g, 42%) and **20ba** (1.39 g, 56%). The analytical sample of **18b**, mp 89.3 °C, was obtained by recrystallization from hexanes: ^{1}H NMR δ 2.16 (s, 6 H), 3.50 (s, 3 H), 7.1–7.25 (m, 3 H); IR 1590, 1540 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43; S, 14.56.

Found: C, 55.51; H, 5.54; N, 25.68; S, 14.82.

The analytical sample of **20ba**, mp 84.8 °C, was obtained by recrystallization from pentanes: ^{1}H NMR δ 2.00 (s, 6 H), 2.84 (s, 3 H), 3.26 (s, 3 H), 6.7–7.0 (m, 3 H); ^{13}C NMR δ 153.1, 148.8, 143.8, 126.7, 126.3, 122.4, 29.5, 27.8, 15.3; IR 1720, 1650 cm^{-1}. Anal. Calcd for $C_{12}H_{15}N_3OS$: C, 57.80; H, 6.06; N, 16.85; S, 12.86. Found: C, 57.91; H, 6.04; N, 16.91; s, 12.72.

***N*-(2,6-Diethylphenyl)-*N*-methyl-1,2,3,4-thiatriazol-5-amine (18d) and 5-[(2,6-Diethylphenyl)imino]-2,4-dimethyl-1,2,4-thiadiazolidin-3-one (20da).** The procedure described for **18b** and **20ba** was used on 10-mmol scale of **1d**. Chromatography did not separate the two products completely, but gave **18d** (0.41 g, 16%) as an oil, a mixture of **18d** and **20da** (1.38 g) which was calculated from the integration of the NCH_3 peaks in the ^{1}H NMR spectrum to consist of **18d** (1.54 mmol, 15%) and **20da** (3.60 mmol, 36%), and pure **20da** (0.68 g, 24%) as an oil. Characterization of **18d**: ^{1}H NMR δ 1.18 (t, 6 H), 2.50 (q, 4 H), 3.55 (s, 3 H), 7.1–7.45 (m, 3 H); ^{13}C NMR δ 178.2, 138.4, 127.5, 125.5, 38.6, 21.0, 12.1; IR 1690, 1635 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_4S$: C, 58.03; H, 6.49; N, 22.56; S, 12.91. Found: C, 58.75; H, 6.75; N, 21.86; S, 13.41. Characterization of **20da**: ^{1}H NMR δ 1.19 (t, 6 H), 2.50 (q, 4 H), 3.02 (s, 3 H), 3.40 (s, 3 H), 7.01 (s, 3 H); IR 1725, 1640 cm^{-1}. Anal. Calcd for $C_{14}H_{19}N_3OS$: C, 60.62; H, 6.90; N, 15.15; S, 11.56. Found: C, 60.39; H, 7.04; N, 15.08; S, 12.42.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N*-methyl-1,2,3,4-thiatriazol-5-amine (18e) and 5-[[2,6-Bis(1-methylethyl)phenyl]imino]-2,4-dimethyl-1,2,4-thiadiazolidin-3-one (20ea).** The procedure described for **18b** and **20ba** was used on a 20-mmol scale for **1e**. An aliquot of the reaction mixture was examined by ^{1}H NMR and found to contain a 1:2.42 ratio of **18e**:**20ea**. Chromatography on silica gel with 5:1 hexanes/EtOAc gave **18e** (1.70 g, 31%) and **20ea** (3.00 g, 49%). Characterization of **18e**: mp 100.4 °C; IR 1690, 1640 cm^{-1}. Anal. Calcd for $C_{14}H_{20}N_4S$: C, 60.83; H, 7.29; N, 20.27. Found: C, 60.80; H, 7.20; N, 20.95. Characterization of **20ea**: mp 114.4 °C; ^{13}C NMR δ 153.2, 148.6, 141.4, 137.2, 123.1, 121.5, 29.6, 27.9, 25.9, 21.3; IR 1725, 1650, 1590 cm^{-1}. Anal. Calcd for $C_{16}H_{23}N_3OS$: C, 62.91; H, 7.59; N, 13.76. Found: C, 62.99; H, 7.28; N, 13.99.

***N*-(2,6-Dimethylphenyl)-*N*-methyl-1,2,3,4-thiatriazol-5-amine (18b) and 5-[(2,6-Dimethylphenyl)imino]-2-ethyl-4-methyl-1,2,4-thiadiazolidin-3-one (20bb).** The procedure described for **18b** and **20ba** was used on a 20.0-mmol scale. Chromatography with 9:1 toluene/EtOAc gave **18b** (1.65 g, 38%) and **20bb** (2.93 g, 55.0%) as an oil. Characterization of **20bb**: ^{1}H NMR δ 1.10 (t, 3 H), 2.12 (s, 6 H), 3.38 (s, 3 H), 3.60 (q, 2 H), 6.8–7.2 (m, 3 H). Anal. Calcd for $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.51; N, 15.96; S, 12.17. Found: C, 59.30; H, 6.50; N, 16.10; S, 12.65.

[4-(4-Chloro-2-methylphenyl)-2-methyl-3-thioxo-1,2,4-thiadazolidin-5-ylidene]methylurea (22). A solution of **8ga** (2.56 g, 10.0 mmol), methyl isothiocyanate (0.80 g, 11 mmol), and Et_3N (10 drops) in 40 mL of THF was stirred at ambient temperature for 68 h. The solids (**8ga**, 1.03 g, 40%) were filtered and washed with THF. The filtrate was evaporated to dryness, and the residue was chromatographed on a size C Merck prepacked silica gel column with 1:1 hexanes/EtOAc (sample applied in 10 mL of $CHCl_3$) to yield **22** (2.00 g, 61%). The analytical sample, mp 179.2 °C, was obtained by recrystallization from MeOH: ^{1}H NMR δ 2.11 (s, 3 H), 2.80 (d, 3 H), 3.50 (s, 3 H), 5.62 (q, 1 H), 7.0–7.4 (m, 3 H); ^{13}C NMR (DMSO-d_6) δ 172.6, 166.1, 164.6, 138.4, 136.3, 134.0, 131.0, 130.6, 127.2, 34.8, 27.0, 17.0; IR 3430, 1630 cm^{-1}. Anal. Calcd for $C_{12}H_{13}ClN_4OS_2$: C, 43.83; H, 3.98; Cl; 10.78; N, 17.04; S, 19.50. Found: C, 43.65; H, 3.97; Cl, 10.93; N, 17.24; S, 19.39.

(2,4-Dimethyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene)carbamic Acid Phenyl Ester (28). Phenyl chloroformate (21.9 g, 0.140 mol) was added dropwise to a solution of KNCS (14.6 g, 0.150 mol) in 150 mL of acetone. The suspension was refluxed for 10 min and cooled to room temperature, **25** (12.34 g, 0.140 mol) was added, and the mixture was stirred for 3 h. It was poured into ice water, the precipitate was collected, partly dried on the filter, and then stirred with 400 mL of CH_2Cl_2. The solids were filtered to give almost pure **26** (3.60 g, 10%, TLC with 3:1 hexanes/EtOAc). The filtrate was dried over Na_2SO_4 and evaporated to dryness, and the residue was recrystallized from EtOAc (150 mL) to give **27** (4.83 g, 20%), mp 209.7 °C. Further concentration gave 8.0 g of a mixture of **26** and **27**, which cyclized to essentially pure **27** during 3 weeks at ambient temperature.

Compound **26** (2.67 g, 10.0 mmol), partly dissolved in absolute EtOH (75 mL), was treated with Br_2 (1.60 g, 10.0 mmol). After 10 min the solids were filtered and dried to yield **28** (2.06 g, 78%), mp 137.7 °C. The analytical sample, mp 138.8 °C, was obtained by recrystallization from hexanes with a trace of EtOAc: ^{1}H NMR δ 3.12 (s, 3 H), 3.48 (s, 3 H), 7.0–7.5 (m, 5 H); IR 1725, 1625 cm^{-1}. Anal. Calcd for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.84; S, 12.09. Found: C, 49.75; H, 4.11; N, 15.95; S, 12.01.

(2,4-Dimethyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene)-methylurea (12faa). A solution of **28** (1.33 g, 5.00 mmol) in 10 mL of THF was treated with 40% aqueous CH_3NH_2. After 10 min the precipitate was filtered, washed with water, and dried to yield **12faa** (0.76 g, 75%), mp 188.3 °C.[18] The IR spectrum was identical to that for the material prepared from **1a** and **2a**.

Kinetics. A solution of **1** (0.5 M), 1 equiv of **2**, and a catalytic amount of Et_3N in $CDCl_3$ containing 0.5–1.0% TMS was placed in an NMR tube, and the solution was analyzed by ^{1}H NMR spectroscopy (90 MHz). The concentrations of the products were followed by integration of the peaks which were separated the best in **1**, **3**, and **12**.

Acknowledgment. We thank the Physical and Analytical Chemistry unit of The Upjohn Company for the elemental analyses and Dr. William Watt for collecting the X-ray data.

Supplementary Material Available: X-ray crystallography data for **12baa** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(18) The reported (ref 1) mp is 188.0 °C.