The Reactivity of (*Z*)-5-Acetyl-3-aryl-2,3-dihydro-2-[(thioacyl)methylene]-1,3,4-thiadiazoles: A Surprising Base-Induced Conversion into 3-(*N*-arylamino)thiophenes

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Dedicated to Professor Rolf Huisgen

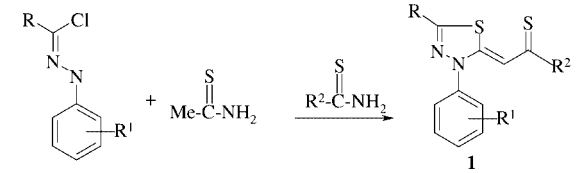
Keywords: Cycloaddition / Heterocycles / Ketene imines / Sulfur

We report the reactivity shown by two classes of rarely investigated heterocycles, the 5-acetyl-2,3-dihydro-3-phenyl-2-(phenylmethylene)-1,3,4-thiadiazoles (**6**) and the 5-alkanoyl-3-aryl-2,3-dihydro-2-[(thioacyl)methylene]-1,3,4-thiadiazoles **1a**–**e**. In both cases, strong bases promote cleavage of the thiadiazole ring with loss of thiocyanate anion, generating *N*-arylketeneimines and *N*-aryl(thioacyl)keteneimines **5**, respectively. These very reactive species undergo either nucleophilic addition or [4+2] cycloaddition reactions involving the thioacyl function. The most surprising result was found in the reactions of the 5-acetyl-3-aryl-2,3-dihydro-2-[(thioacyl)methylene]-1,3,4-thiadiazoles **1a**,**d**,**e**, which afford 3-(arylamino)thiophenes **2**, **10**, and **14** as the main products. This serendipitous transformation, which seems to be rather general, probably involves an intermediate step in which the acetyl group of the substrates is converted into ketene.

Introduction

Some years ago we described an easy route to 5-substituted (*Z*)-3-aryl-2,3-dihydro-2-[(thioacyl)methylene]-1,3,4-thiadiazoles (**1**) involving the reaction of α-halohydrazones with thioamides in refluxing toluene solutions[1] (Scheme 1). The availability of these uncommon compounds stimulated the investigation of their chemical behavior, which appeared unusual from the preliminary experiments. For instance, the thiocarbonyl group exhibited a total lack of reactivity toward the typical reagents of the carbonyl function, like lithium aluminum hydride and hydrazines.

This paper reports the surprising results found in the reactions of 5-alkanoyl-3-aryl-2,3-dihydro-2-[(thioacyl)methylene]-1,3,4-thiadiazoles **1a**,**c**,**d**,**e** with sodium alkoxides and in the cycloaddition reactions of **1a**, **1f**, and **1g** with dimethyl acetylenedicarboxylate.



1	a	b	c	d	e	f	g
R	CO-Me	Ph	CO-Et	CO-Me	CO-Me	COOEt	Ph
R^1	H	H	H	4-Me	H	3,5-diMe	H
R^2	Me	Me	Me	Me	Ph	Me	Ph

Scheme 1

Results and Discussion

Reactions with Alkoxides

Briefly heating of a solution of **1a** and sodium methoxide in methanol under reflux afforded a mixture of three products (Scheme 2), which were isolated in a pure state by chromatography.

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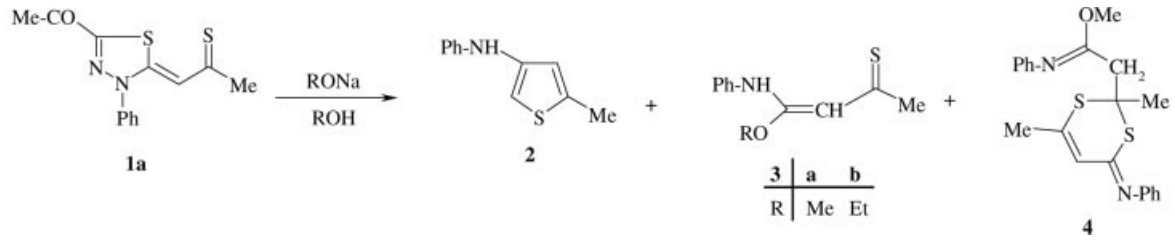
  DOI: 10.1002/ejoc.200300048



Scheme 2

Structures **2**, **3a**, and **4** were assigned on the basis of analytical and spectroscopic data and chemical evidence. 5-Methyl-3-(*N*-phenylamino)thiophene (**2**), the main reaction product (25% isolated yield), was desulfurized with Raney nickel in dioxane solution under reflux to give the *N*-(2-pentyl)aniline that is identical to an authentic sample prepared by catalytic hydrogenation of 2-(*N*-phenylimino)pentane. Acid hydrolysis of methyl *N*-phenylthioacetacetimidate (**3a**) in 10% hydrochloric acid solution under reflux gave aniline, methanol and acetone (GC). The structural assignment to the minor reaction product, methyl *N*-phenyl-2-[2,6-dimethyl-4-(phenylimino)-1,3-dithi-5-en-2-yl]acetimidate (**4**), is based on analytical, MS, ^{1}H, and ^{13}C NMR spectroscopic data, which ruled out all other isomeric structures as options. Conjugation between the phenyl and imino groups would be responsible for the prototropic rearrangement of the product formed originally.

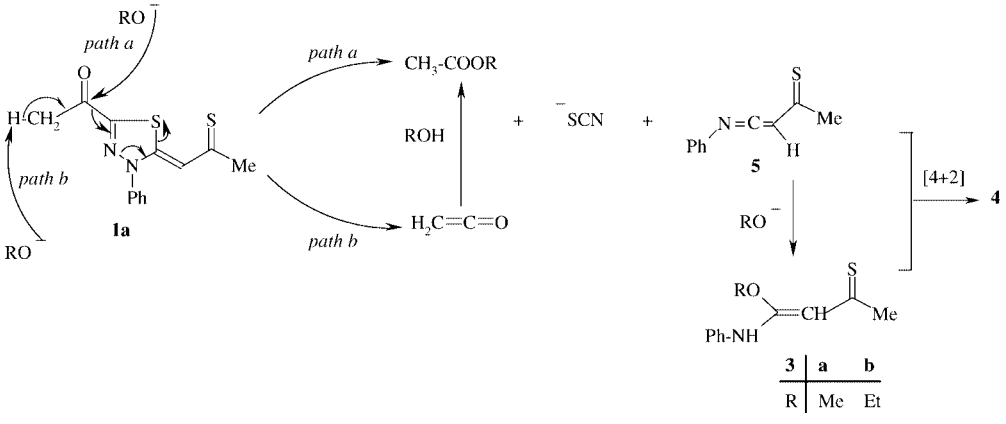
Similar results were obtained in the reaction of **1a** with sodium ethoxide, which gave **2** and **3b**, while a compound corresponding to **4** was not detected.

With regard to the reaction mechanisms governing the formation of **2**, **3a**,**b**, and **4**, proof that the acetyl group in position 5 is the critical reaction center of **1a** was inferred from the total lack of reactivity of 2,3-dihydro-3,5-diphenyl-2-[(thioacetyl)methylene]-1,3,4-thiadiazole (**1b**) and 3-(3,5-dimethylphenyl)-5-ethoxycarbonyl-2,3-dihydro-2-[(thioacetyl)methylene]-1,3,4-thiadiazole (**1f**), in which this function is missing. Compounds **3** and **4** might be the products of different reactions of a common intermediate, the *N*-phenyl(thioacetyl)keteneimine (**5**) (Scheme 3).

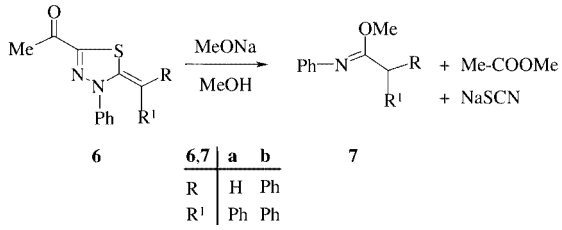
This compound might be formed by two different, and probably concurrent, alkoxide-promoted mechanisms, both of which involve thiadiazole ring opening and loss of a thiocyanate anion. The former involves nucleophilic attack of the alkoxide anion at the carbonyl group of **1a** (*path a*), while the latter develops through abstraction of a hydrogen atom from the acetyl group followed by ketene formation and its rapid conversion into methyl (or ethyl) acetate (*path b*). Both methyl (or ethyl) acetate (GC) and thiocyanate anion (colorimetric test) were detected in the reaction mixture. The (thioacetyl)keteneimine **5** could undergo either a further alkoxide attack, affording **3a**,**b**, or give **4** through a [4+2] cycloaddition process involving the heterodiene system of **5** and the thiocarbonyl group of **3a** as the dienophilic unit. It is known that keteneimines undergo both nucleophilic additions at the imino group's carbon atom[2] and [4+2] cycloaddition reactions with the thiocarbonyl group.[3]

The formation of a keteneimine similar to **5** by alkaline cleavage of a 5-acetyl-2-methylenethiadiazole system was demonstrated in the case of the structurally simpler substrates **6a**,**b**. Their reactions with sodium methoxide in methanol gave the products **7a**,**b**, derived from the nucleophilic attack of the methoxide anion onto a keteneimine intermediate, together with methyl acetate and sodium thiocyanate (Scheme 4). These reactions were found to proceed at a much slower rate than that of **1a**, since the "mesobicycloisomerism"[4] associated with the presence of the thiocarbonyl group enhances the electronic demand of the thiadiazole ring and, thus, makes the acetyl group more electrophilic.

As for the formation of the 5-methyl-3-(phenylamino)thiophene (**2**), the mechanistic suggestion must answer two questions, both related to the observation that the longest



Scheme 3



6 | 6,7 | a | b | 7

R	H	Ph
R¹	Ph	Ph

Scheme 4

sequence of carbon atoms is four in the starting material **1a**, but it is five in the reaction product **2**. Firstly, it is crucial to check whether the atom sequence constituted by the (thioacetyl)methylene group, the C^2 atom and the phenyl-substituted N^3 nitrogen atom of the thiadiazole ring of **1a** would generate the Me−*C*^{5}(−S−)C^4−C^3−*N*HPh skeleton of **2** without rearrangement. If so, the C^2 atom of the thiophene ring would be the added member of the carbon sequence in **2**; b) a further point was to identify which carbon atom of **1a** becomes the fifth atom (C^2) of the five-carbon atom sequence in **2**.

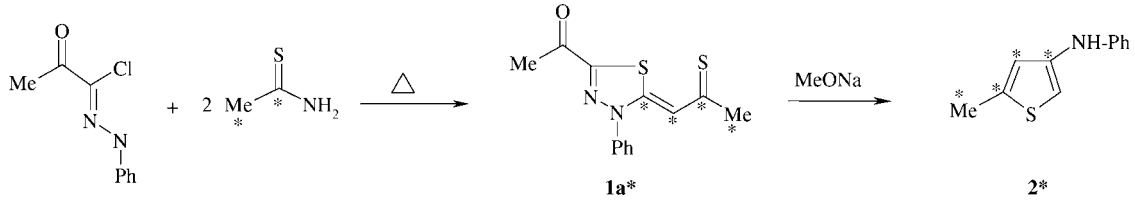
We answered the former questions by preparing the ^{13}C-labeled **1a*** (5% isotopic abundance), starting from 1-chloro-1-phenylhydrazono-2-propanone and [1,2-^{13}C]thioacetamide. The latter was prepared starting from commercially available [1,2-^{13}C]acetic acid (5% isotopic abundance), which was converted into labeled acetamide by reaction with urea at 180 °C. The amide was then converted into the corresponding labeled thioamide by reaction with phosphorus pentasulfide in toluene solution under reflux. The ^{13}C NMR spectrum of **1a*** clearly showed selective labeling at all the carbon atoms of the (thioacyl)methylene system and at the C^2 carbon atom of the heterocyclic ring. Coupling is observed between the methyl and thiocarbonyl groups and also between the heterocyclic C^2 and the *exo*-methylenic carbon atoms.

The reaction of **1a*** with sodium methoxide in methanol solution gave the thienylaniline **2*** in which the methyl group and the C^3, C^4, and C^5 carbon atoms of the ring were labeled, while only the C^2 carbon atom was found to be unlabeled. The same coupling pattern found in the ^{13}C NMR spectrum of **1a*** was still present in the spectrum of **2***, which proves that the whole labeled sequence of **1a*** was transferred intact into **2*** (Scheme 5).

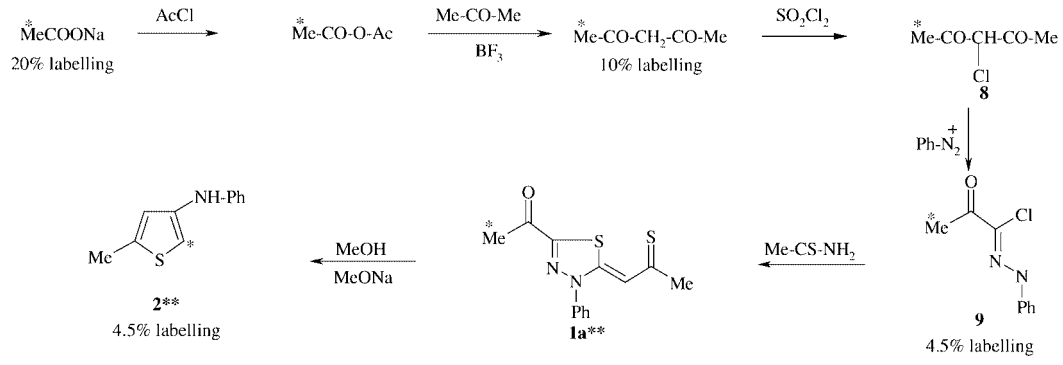
The next step was to identify the carbon atom of **1a** that is converted into the C^2 carbon atom of the thiophene ring of **2**. For this purpose we prepared a new ^{13}C-labeled **1a****, carrying the labeling on the methyl group of the 5-acetyl substituent. This carbon atom was envisaged, on the basis of its oxidation level, to be the most probable candidate amongst the two remaining options.

The synthesis of **1a**** was accomplished starting from commercially available sodium [2-^{13}C]acetate (isotopic abundance ca. 20%), which was converted into acetic anhydride by treatment with unlabeled acetyl chloride and then into acetylacetone (isotopic abundance ca. 10%)[5] by BF_3-catalyzed reaction with unlabeled 2-propanone. Chlorination with sulfuryl chloride, followed by coupling with phenyldiazonium chloride in neutral solution gave [3-^{13}C]-1-chloro-1-phenylhydrazono-2-propanone (**9**) (isotopic abundance 4.5%) (Scheme 6). The latter compound led to labeled thiadiazole **1a**** by reaction with thioacetamide under the usual experimental conditions; when **9** was treated with sodium methoxide the product was anilinothiophene **2****, which was labeled exclusively in position 2 of the heterocyclic ring.

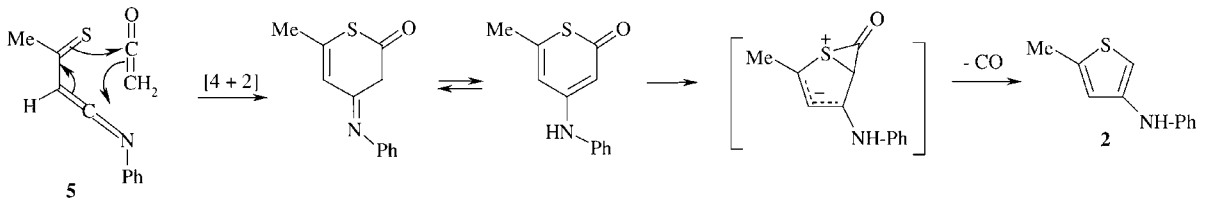
On the basis of these results, we hypothesize the mechanism for the origin of **2** to be that the ketene formed by



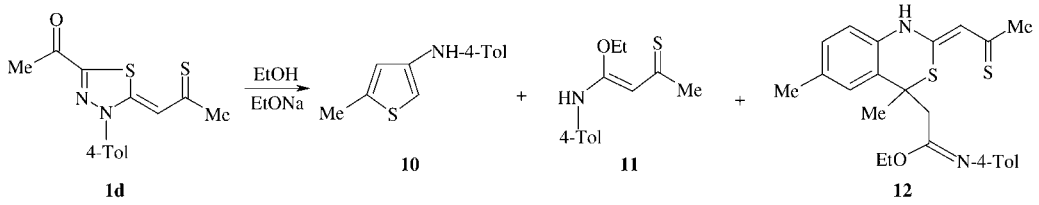
Scheme 5



Scheme 6



Scheme 7



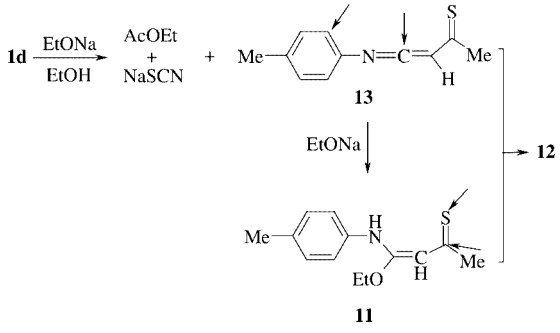
Scheme 8

hydrogen abstraction from **1a** (*path b* of Scheme 3) behaves as a dienophile in a [4+2] cycloaddition reaction with the (thioacetyl)keteneimine **5** produced in the same process, to give the 4-anilino-6-methyl-2*H*-thiopyran-2-one as an intermediate, which would suffer extrusion of carbon monoxide to afford the aromatic anilinothiophene **2** (Scheme 7).

The thermal transformation of 2,2′-disubstituted 2*H*-thiopyrans into thiophene derivatives, with expulsion of the carbon atom in position 2 from the ring, has been documented in the literature for a long time, even though the mechanism of this transformation has not been fully elucidated yet.[6] An interesting suggestion involves a bicyclic ylide species, either as a formal intermediate or as a transition state.[7]

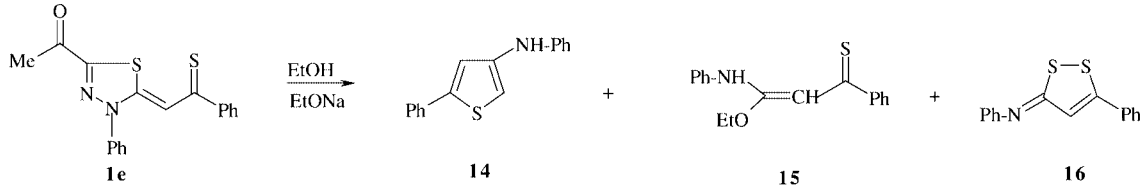
Some experimental support for the intermediate formation of ketene is given by the observation that the yields in **2** increased up to 50% when non-nucleophilic bases (NaH, DBN) in THF were employed instead of sodium methoxide in methanol. The reaction is driven exclusively along *path b* of Scheme 3, and the reaction of the ketene toward the nucleophilic addition cannot occur. Further support to this mechanistic hypothesis is supplied by the observation that the reaction of the 5-propionyl-substituted thiadiazole **1c** with sodium methoxide does not produce the anilinothiophene derivative (only **3a** and **4** are formed), since the lower acidity of the propionyl group, in comparison with the acetyl group, depresses the ketene formation (*path b* in Scheme 3). The reaction with alkoxides was extended to substrate **1d** with similar results (Scheme 8).

Structural assignments of the reaction products **10**, **11**, and **12** are based on analytical and spectroscopic data, which, in the cases of **10** and **11**, were found to be very similar to those displayed by **2** and **3a**. The formation of the benzothiazine derivative **12**, resulting from the [4+2] cycloaddition of the (thioacyl)keteneimine **13** and the thiocarbonyl function of **11**, is not surprising, since literature data indicate that *N*-phenylketeneimines carrying electron-donor substituents (Me, OMe) on the phenyl ring undergo [4+2] cycloaddition reactions with thioketenes that involve the imino group and the ortho position of the aromatic system[3] (Scheme 9; arrows indicate the cycloaddition termini).



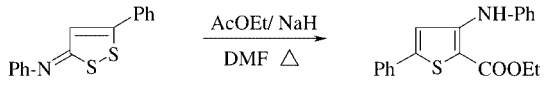
Scheme 9

[(Thiobenzoyl)methylene]thiadiazole **1e** showed a behavior in line with that exhibited by **1a** and **1d**. Its reaction with sodium ethoxide gave the anilinothiophene derivative **14**, the imino ester **15**, and the known compound 5-phenyl-3-phenylimino-3*H*-1,2-dithiole (**16**), which was identified by comparison with an authentic sample prepared according to the literature.[8] (Scheme 10)



Scheme 10

The formation of **14** and **15** was expected, while the lack of [4+2] cycloaddition products was attributed to the lower reactivity displayed by the thiobenzoyl unit in the cycloaddition process relative to the thioacetyl group. The dithiole derivative **16** would result from an alternative thiadiazole ring-opening that involves loss of cyanide ion. We considered checking whether product **16** could be an intermediate in the formation of the anilinothiophene **14**. We discarded this possibility, since we found that **16** is stable toward a solution of ethyl acetate and sodium methoxide in methanol. Interestingly, its reaction with ethyl acetate in the presence of sodium hydride in DMF solution at 80 °C gave the ethyl 3-anilino-5-phenyl-2-thiophenecarboxylate (**17**), though in modest yields, while the anilinothiophene derivative **14** could not be detected (Scheme 11).

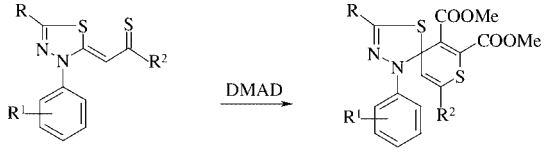


16 **17**

Scheme 11

Cycloaddition Reactions

Reaction of [(thioacyl)methylene]thiadiazoles **1a**, **1f**, and **1g** with dimethyl acetylenedicarboxylate (DMAD) were carried out in chlorobenzene solution under reflux. Surprisingly, the reaction rates were strongly enhanced upon UV irradiation, which allowed the reaction to occur at room temperature in dichloromethane solution (Scheme 12). The structure of the reaction products was elucidated in the case of **18f** by single-crystal X-ray diffraction analysis (Figure 1).



1 **18**

1, 18	a	f	g
R	CO-Me	COOEt	Ph
R^1	H	3,5-diMe	H
R^2	Me	Me	Ph

Scheme 12

Compounds **18a**,**f**,**g** belong to the already known, although rarely described, class of the spiro[3*H*-1,3,4-thiadiazoline-2,4′-4*H*-thiopyran]s, which generally are prepared by addition of diazomethane to thioxanthene-9-, thiopyran-4-, and dihydrothiopyran-4-thiones.[9] The synthetic approach starting from [(thioacyl)methylene]thiadiazoles with dimethyl acetylenedicarboxylate is, however, the most flexible scheme available for assembly of this heterocyclic framework, since it represents a good strategy to introduce suitable reactive functions on either ring.

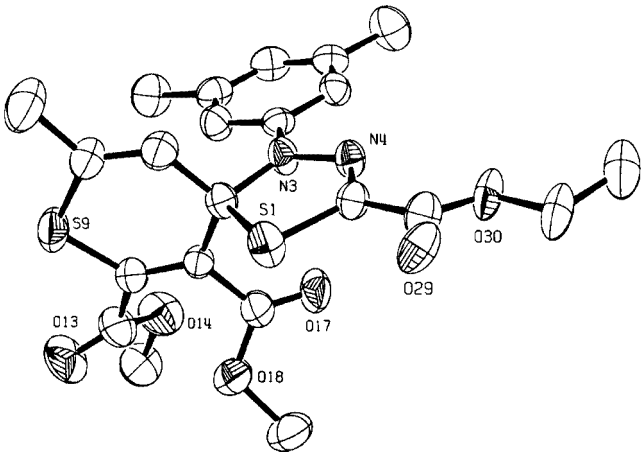


Figure 1. Crystal structure of **18f**; only the most populated conformation of the disordered methoxycarbonyl and ethoxycarbonyl groups is shown; hydrogen atoms have been omitted, ellipsoids are drawn at a 50% probability level

Conclusions

The results reported in this paper illustrate the reactivity shown by two classes of rarely investigated heterocycles, the 5-acetyl-3-aryl-2,3-dihydro-2-methylene-1,3,4-thiadiazoles **6a**,**b** and the 5-alkanoyl-3-aryl-2,3-dihydro-2-[(thioacyl)-methylene]-1,3,4-thiadiazoles **1a**,**c**,**d**,**e**. These substrates are now easily available through short and reliable reaction sequences, starting from inexpensive starting materials. Their reactivity toward strong nucleophilic bases is interesting. In both cases the thiadiazole ring undergoes an easy cleavage with loss of the thiocyanate anion: in the former case, *N*-arylketeneimines are produced, while in the latter, *N*-aryl-(thioacyl)keteneimines **5** are generated. These very reactive species undergo either nucleophilic addition or [4+2] cycloaddition reactions involving the thioacyl function. The base-promoted ring openings of 5-acetyl-2-methylene-1,3,4-thiadiazoles and 5-acetyl-2-[(thioacyl)methylene]-1,3,4-thiadiazoles probably represent the most efficient methods to produce keteneimines.

The most surprising result was that found in the reactions of 5-acetyl-3-aryl-2,3-dihydro-2-[(thioacyl)methylene]-1,3,4-thiadiazoles **1a**,**d**,**e** with strong, non-nucleophilic bases, which afford 3-anilinothiophenes **2**, **10**, and **14** as the main reaction products. This serendipitous transformation, which seems to be rather general, probably involves the intermediate conversion of the acetyl group of the substrates into ketene.

Experimental Section

General Remarks: Melting points were recorded with a Büchi apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Varian XL 300 spectrometer using $CDCl_3$ as the solvent. Mass spectra were recorded with a Vg 70-70 Eq-Hf spectrometer (DIS-EI). Irradiation was carried out with an HPK-

125 W Philips, high-pressure mercury vapor lamp, in a preparative photochemical reactor equipped with a Pyrex double-walled immersion well for water-cooling of the lamp.

Reaction of 1,3,4-Thiadiazoles with Sodium Alkoxides. General Procedure: The 1,3,4-thiadiazoles **1a**−**e** and **6a**,**b** (1 mol) were added to a solution prepared by dissolving sodium (1.3 mol) in MeOH or EtOH. The solution was heated under reflux, then poured in water and exhaustively extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and the solvents evaporated to dryness to give a residue that was usually column-chromatographed on silica gel (eluent: CH_2Cl_2).

Reaction of 1a with MeONa: The reaction was complete within 25 min. The first product eluted was **2** (25% yield), obtained as a pale pink solid, which was triturated with hexane; m.p. 75 °C. ^{1}H NMR: δ = 7.23 (d, *J* = 7.7 Hz, 2 H), 6.95 (t, *J* = 7.93 Hz, 2 H), 6.84 (t, *J* = 7.3 Hz, 1 H), 6.60 (s, 1 H), 6.47 (s, 1 H), 4.61 (s, NH), 2.44 (s, 3 H) ppm. ^{13}C NMR: δ = 144.6, 140.6, 139.3, 129.3, 121.2, 119.7, 115.5, 104.02, 15.7 ppm. MS: *m*/*z* = 189. $C_{11}H_{11}NS$ (189.3): calcd. C 70.84, H 5.82, N 7.41; found C 70.91, H 5.82, N 7.47. The second product eluted was **3a**, obtained as a red oil. ^{1}H NMR: δ = 11.1 (s, NH), 7.27 (m, 5 H), 6.10 (s, 1 H), 3.94 (s, 3 H), 2.66 (s, 3 H) ppm. The third product eluted was further purified by chromatography to give **4** as a yellow solid that was crystallized from diisopropyl ether/benzene (95:5); m.p. 134 °C. ^{1}H NMR: δ = 7.13 (m, 11 H), 3.80 (s, 3 H), 3.06 and 3.43 (2 d, *J* = 14.5 Hz, 2 H), 1.96 (s, 3 H), 1.46 (s, 3 H) ppm. ^{13}C NMR: δ = 191.7, 158.1, 147.4, 141.7, 138.7, 129.5, 129.2, 128.8, 128.4, 126.85, 123.3, 121.3, 67.6, 53.1, 37.3, 27.1, 22.0 ppm.

Reaction of 1a with EtONa: The reaction was complete within 40 min. The first product eluted was **2** (24%); analytical and spectroscopic data are identical to those exhibited by the sample obtained in the reaction of **1a** with MeONa. The second product eluted was rechromatographed to give **3b** as an orange oil: ^{1}H NMR: δ = 15.18 (s, NH), 7.12 (m, 5 H), 6.09 (s, 1 H), 4.06 (q, 2 H), 2.61 (s, 3 H), 1.46 (t, 3 H) ppm.

Reaction of 1c with MeONa: The reaction mixture was heated under reflux for 10 min and then stirred at room temp. for 2 h. Compounds **3a** and **4** were isolated by column chromatography and their analytical and spectroscopic data are identical to those obtained in the reaction of **1a** with MeONa.

Reaction of 1d with EtONa: The reaction was complete within 25 min. The first product eluted was **10** (26%), obtained as a pale yellow solid that was crystallized from hexane; m.p. 104 °C. ^{1}H NMR: δ = 7.03 (d, *J* = 9 Hz, 2 H), 6.87 (d, *J* = 9 Hz, 2 H), 6.55 (s, 1 H), 6.39 (s, 1 H), 5.52 (s, NH), 2.44 (s, 3 H), 2.27 (s, 3 H) ppm. MS: *m*/*z* = 203. $C_{12}H_{13}NS$ (203.3): calcd. C 70.90, H 6.45, N 6.89; found C 70.92, H 6.50, N 7.02. The second product eluted was **11**, obtained as a brown solid that was triturated with hexane. ^{1}H NMR: δ = 15.10 (s, NH), 7.28 (d, *J* = 4.8 Hz, 2 H), 7.13 (d, *J* = 4.8 Hz, 2 H), 6.05 (s, 1 H), 4.24 (q, *J* = 4 Hz, 2 H), 2.61 (s, 3 H), 2.31 (s, 3 H), 1.42 (t, *J* = 4 Hz, 3 H) ppm. MS: *m*/*z* = 235. The third product eluted was **12**, obtained as a red oil. ^{1}H NMR: δ = 6.95 (m, 6 H), 6.55 (d, *J* = 8.9 Hz, 2 H), 4.21 (q, *J* = 5.8 Hz, 2 H), 3.02 and 3.40 (2 d, *J* = 14.7 Hz, 2 H), 2.31 and 2.37 (2 s, 6 H), 1.95 (s, 3 H), 1.45 (s, 3 H), 1.31 (t, *J* = 5.8 Hz, 3 H) ppm. MS: *m*/*z* = 424.

Reaction of 1e with EtONa: The reaction was complete within 15 min. The aqueous layer was treated with 10% HCl solution; a yellow solid precipitated, which was dissolved in CH_2Cl_2, dried (Na_2SO_4) and the solvents were evaporated to dryness to give **16** as a red solid; m.p. 125 °C; the ^{1}H NMR spectrum, which shows a multiplet at δ = 7.43 ppm, is identical to that exhibited by the sample obtained by independent synthesis.[5] MS: *m*/*z* = 266. The organic phase was worked up according to the usual procedure; the first product that eluted was **14** (26%), obtained as an orange oil that solidified when treated with hexane. ^{1}H NMR: δ = 7.58 (d, *J* = 10.07 Hz, 2 H), 7.32 (m, 5 H), 7.15 (d, *J* = 2.13 Hz, 1 H), 7.00 (d, *J* = 7.63 Hz, 2 H), 6.79 (t, *J* = 7.47 Hz, 1 H), 6.68 (d, *J* = 1.53 Hz, 1 H), 5.68 (s, NH) ppm. ^{13}C NMR: δ = 129.4, 128.85, 127.7, 152.53, 120.02, 118.8, 115.8, 106.1 ppm. The second product that eluted was **15**, which was isolated as a red oil. ^{1}H NMR: δ = 10.76 (s, NH), 7.49 (m, 10 H), 6.50 (s, 1 H), 4.36 (q, *J* = 6.8 Hz, 2 H), 1.49 (t, *J* = 6.8 Hz, 3 H) ppm. MS: *m*/*z* = 283.

Reaction of 16 with NaH: EtOAc (2 mL) and NaH (0.108 g, 60% suspension) were added to a solution of **16** (0.5 g) in DMF (10 mL). The solution was heated under reflux for 10 min, and then stirred at room temp. for 16 h. The solvent was evaporated under reduced pressure and then the residue was diluted with H_2O and extracted exhaustively with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and the solvents evaporated to dryness to give a residue that was triturated with diisopropyl ether to give **16** as a yellow solid, which was collected by filtration. The filtrate was chromatographed on silica gel ($CHCl_3$) to give a yellow oil that, after treatment with hexane, provided **17** (0.07 g, 11.4%) as a solid; m.p. 90 °C. ^{1}H NMR: δ = 7.61 (m, 2 H), 7.31 (m, 8 H), 7.07 (t, *J* = 7 Hz, 1 H), 4.36 (q, *J* = 7.5 Hz, 2 H), 1.37 (t, *J* = 7.5 Hz, 3 H) ppm. MS: *m*/*z* = 323. $C_{19}H_{17}NO_2S$ (323.3): calcd. C 70.56, H 5.30, N 4.33; found C 70.98, H 5.26, N 4.33.

Reaction of 6a with MeONa: The reaction was complete within 8 h. The crude reaction product was triturated with hexane to give methyl **7a** (32.9%); m.p. > 210 °C. ^{1}H NMR: δ = 7.31 (m, 5 H), 7.07 (m, 3 H), 6.77 (d, *J* = 8 Hz, 2 H), 3.79 (s, 3 H), 3.5 (s, 2 H) ppm. ^{13}C NMR: δ = 161.7, 148.5, 135.8, 129.0, 128.9, 128.4, 126.6, 123.0, 121.4, 53.5, 36.04 ppm. MS: *m*/*z* = 225.

Reaction of 6b with MeONa: The reaction was complete within 4 h. The crude reaction product was triturated with hexane to give **7b** (30.2%); m.p. 72 °C. ^{1}H NMR: δ = 7.30 (m, 8 H), 7.16 (d, 4 H), 7.08 (t, 1 H), 6.78 (d, 2 H), 5.14 (s, 1 H), 3.87 (s, 3 H) ppm. MS: *m*/*z* = 301. $C_{21}H_{19}NO$ (301.4): calcd. C 83.69, H 6.35, N 4.65; found C 83.71, H 6.32, N 4.50.

Preparation of [1,2-^{13}C]Acetamide: A mixture of [1,2-^{13}C]acetic acid having 5% isotopic abundance (8.15 g) and urea (7.25 g) was heated at 200 °C on an oil bath. Heating was continued until gas evolution stopped, and then the mixture was distilled to give the title compound (b.p. 200 °C, 5.70 g, 71%). ^{13}C NMR: δ = 173.2 (s + d, *J* = 130 Hz, C=O), 22.6 (s + d, *J* = 130 Hz, CH_3).

Preparation of [1,2-^{13}C]Thioacetamide: A mixture of [1,2-^{13}C]acetamide having 5% isotopic abundance (5.65 g), P_2S_5 (4.40 g) and K_2S (9.50 g) in toluene was heated at 75−80 °C with stirring for 1 h, and then the toluene was decanted. This sequence was repeated seven times. The reaction solvents were evaporated to dryness to give a residue that was added to the white solid that had precipitated from toluene, and then this mixture was chromatographed on silica gel (CH_2Cl_2/EtOAc, 7:3). The last fractions gave [1,2-^{13}C]thioacetamide (1.27 g, 17.6%). ^{13}C NMR: δ = 206.9 (s + d, *J* = 160 Hz, C=S), 33.0 (s + d, *J* = 160 Hz, CH_3) ppm.

Preparation of (*Z*)-[2,1′,2′,3′-^{13}C]-5-Acetyl-2,3-dihydro-3-phenyl-2-[(thioacetyl)methylene]-1,3,4-thiadiazole (1a*): 1-Chloro-1-(phenylhydrazono)-2-propanone (1.10 g) was added to a solution of [1,2-

^{13}C]thioacetamide having 5% isotopic abundance (1.27 g) in toluene (10 mL) under N_2. The solution was heated under reflux for 4 h with stirring, and then it was poured into water and extracted exhaustively with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and the solvents were evaporated to dryness to give a residue that was chromatographed on silica gel (CH_2Cl_2). The first fractions gave **1a*** (0.22 g, 14.2%) as a red solid; m.p. 188 °C ppm. ^{13}C NMR: δ = 209.05 (s + d, *J* = 160 Hz, C=S), 191.3, 162.5 (s + d, *J* = 300 Hz, C-2), 147.05, 138.0, 130.0, 129.6, 126.0, 108.0 (s + d, *J* = 300 Hz, CH), 37.6 (s + d, *J* = 160 Hz, *CH*$_3$CS), 26.3 ppm.

Reaction of 1a* with MeONa: Compound **1a*** (0.27 g) was added to a solution of MeONa, which was obtained by addition of sodium (0.028 g) to MeOH (3 mL); the solution was heated under reflux for 10 min and then it was concentrated to dryness to give a residue that was treated with water and extracted with CH_2Cl_2. The organic layer was concentrated to dryness to give a residue that was chromatographed on silica gel (eluent: CH_2Cl_2) to give **2a*** (0.01 g, 5.6%). ^{13}C NMR: δ = 144.6, 140.6 (s + d, *J* = 255 Hz, C-4), 139.3 (s + d, *J* = 195 Hz, C-2), 129.2, 121.2 (s + d, *J* = 255 Hz, C-3), 119.7, 115.5, 104.0, 15.7 (s + d, *J* = 195 Hz, CH_3) ppm.

Preparation of [1-^{13}C]-3-Chloroacetylacetone (8): SO_2Cl_2 (1.6 g) was added dropwise to a solution of [1-^{13}C]acetylacetone[5] in CH_2Cl_2 (8 mL) and then the reaction mixture was heated under reflux for 1 h. The solvent was evaporated under reduced pressure and the residue was then employed in the following reaction without any further purification.

Preparation of [3-^{13}C]-1-Chloro-1-phenylhydrazono-2-propanone (9): A solution of $NaNO_2$ (0.62 g) in water (2 mL) was added dropwise to a solution of aniline (0.84 g) in 18% aqueous HCl (6 mL) while keeping the temperature below 5 °C. The solution was neutralized with AcONa·3H_2O and then **8** (1.2 g), having 20% isotopic abundance, and MeOH (15 mL) were added. The suspension was stirred at room temp. for 12 h and then the MeOH was evaporated under reduced pressure. The residue was treated with H_2O, collected by filtration, and then chromatographed on silica gel (CH_2Cl_2). The first fractions gave **9** (1.26 g, 71.8%), having a 5% isotopic abundance, as a yellow solid. ^{13}C NMR: δ = 188.4, 141.3, 129.6, 125.2, 123.6, 114.5, 25.3 ppm.

Preparation of 5-[2′-^{13}C]Acetyl-3-phenyl-2,3-dihydro-2-[(thioacetyl)-methylene]-1,3,4-thiadiazole (1a):** Compound **9** having 10% isotopic abundance (1.25 g) was added to a solution of thioacetamide (1.90 g) in toluene (20 mL) under N_2. The solution was heated under reflux for 4 h with stirring, and then it was poured into water and exhaustively extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and the solvents were evaporated to dryness to give a residue that was chromatographed on silica gel (CH_2Cl_2). The first fractions gave **1a**** as a red solid (0.27 g, 15.3%). The ^{13}C NMR spectrum is identical to that of **1a**.

Reaction of 1a with MeONa:** Compound **1a**** (0.26 g) was added to a solution of MeONa, obtained by reaction of sodium (0.13 g) with MeOH (5 mL); the solution was heated under reflux for 5 h and then concentrated to dryness to give a residue that was treated with water and extracted with CH_2Cl_2. The organic layer was concentrated to dryness to give a residue that was chromatographed on silica gel (CH_2Cl_2) to give **2a**** (0.01 g, 5.6%) ppm. The ^{13}C NMR spectrum is identical to that of **2a**, however with an outstanding increase in the intensity of the C-5 signal.

Reactions of 1a,f,g with Dimethyl Acetylenedicarboxylate (DMAD). General Procedure: A solution of **1a**, **1f**, or **1g** (0.1 g) and DMAD (2 mL) in CH_2Cl_2 (5 mL) was placed in the photochemical reactor. After irradiation for 1−4 h, the solvent and unreacted DMAD were evaporated to dryness to give a residue that was chromatographed on silica gel (CH_2Cl_2).

Reaction of 1a with DMAD: The reaction was complete within 1 h. The first fractions eluted provided a solid that was crystallized from MeOH to give **18a** (53.3%), m.p. 138 °C. ^{1}H NMR: δ = 7.15 (m, 5 H), 5.98 (d, *J* = 1 Hz, 1 H), 3.86 (s, 3 H), 3.64 (s, 3 H), 2.56 (s, 3 H), 2.07 (d, *J* = 1 Hz, 3 H) ppm. MS: *m*/*z* = 418. $C_{19}H_{18}N_2O_5S_2$ (418.48): calcd. C 54.54, H 4.30, N 6.70; found C 54.43, H 4.29, N 6.77.

Reaction of 1f with DMAD: The reaction was complete within 4 h. The first fractions eluted afforded an orange solid that was triturated first with MeOH and then with hexane to give **18f** (60%), m.p. 125 °C. ^{1}H NMR: δ = 6.86 (s, 2 H), 6.66 (s, 1 H), 6.00 (s, 1 H), 4.34 (q, *J* = 7 Hz, 2 H), 3.82 (s, 3 H), 3.60 (s, 3 H), 2.25 (s, 6 H), 2.02 (s, 3 H), 1.36 (t, *J* = 7 Hz, 3 H) ppm. ^{13}C NMR: δ = 164.7, 162.8, 160.0, 141.3, 138.0, 131.7, 129.3, 128.8, 128.0, 124.5, 118.5, 116.0, 85.3, 62.1, 53.3, 52.7, 21.6, 14.2 ppm. MS: *m*/*z* = 476. $C_{22}H_{24}N_2O_6S_2$ (476.56): calcd. C 54.44, H 5.09, N 5.88; found C 54.74, H 5.19, N 5.69.

Reaction of 1g with DMAD: The reaction was complete within 4 h. The first fractions eluted afforded an orange solid that was triturated, first with MeOH and then with hexane, to give **18g** (50.4%), m.p. 117 °C. ^{1}H NMR: δ = 7.43 (m, 13 H), 6.93 (m, 2 H), 6.38 (s, 1 H), 3.85 (s, 3 H), 3.58 (s, 3 H) ppm. ^{13}C NMR: δ = 165.3, 162.6, 143.2, 140.9, 135.8, 132.9, 132.3, 130.9, 129.6, 128.9, 128.1, 126.7, 126.5, 121.4, 118.7, 117.4, 84.3, 53.6, 52.9 ppm. MS: *m*/*z* = 514. $C_{28}H_{22}N_2O_4S_2$ (514.61): calcd. C 65.36, H 4.28, N 5.44; found C 65.60, H 4.30, N 5.35.

X-ray Crystallographic Study of Compound 18f: Crystal data: $C_{22}H_{24}N_2O_6S_2$ (476.55), triclinic, space group $P\bar{1}$, *T* = 293 K, *a* = 9.488(2), *b* = 11.474(1), *c* = 14.400(1) Å, α = 103.50(2), β = 105.81(2), γ = 104.84(2)°, *V* = 1181.9(3) Å^3, *Z* = 2, D_X = 1.339 Mg·m^{-3}, μ(Mo-K_α) = 0.265 mm^{-1}; crystal dimensions 0.33 × 0.20 × 0.16 mm, λ = 0.71073 Å (Mo-K_α radiation, graphite monochromator), Nonius CAD4 diffractometer. Data collection: θ/2θ scan mode, 2θ < 55.0°; 5420 collected reflections [4010 with $I_o > 2\cdot\sigma(I_o)$]. The structure was solved using SIR92[10] and refined by using SHELXL-97[11] by full-matrix least squares based on F_o^2, with weights $w = 1/[\sigma^2(F_o)^2 + (0.0647\cdot P)^2]$, where $P = (F_o^2 + 2\cdot F_c^2)/3$. The two methoxycarbonyl and ethoxycarbonyl groups were rotationally disordered and were refined with soft constraints on both geometry and thermal parameters. H atoms were not refined. The final consistency indexes were *R* = 0.0403 and *wR* = 0.0949 (0.0334 and 0.0924, respectively, for observed reflections), goodness-of-fit = 0.922. The final map ranged between −0.16 and 0.33 e·Å^3. CCDC-190616 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

Prof. C. W. Rees (Imperial College, London) is acknowledged for fruitful discussions and suggestions. The authors are grateful to Dr. M. Luzzini for his great enthusiasm in developing the experimental work. T. Benincori thanks the Dipartimento di Chimica Organica e Industriale of the University of Milan for hospitality.

[1] T. Benincori, E. Brenna, F. Sannicolò, L. Trimarco, T. Pilati, *Gazz. Chim. Ital.* **1993**, *123*, 531−537.

[2] G. R. Krow, *Angew. Chem.* **1971**, *83*, 455−470; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 435.

[3] A. Dondoni, A. Battaglia, F. Bernardi, P. Giorgianni, *J. Org. Chem.* **1980**, *45*, 3773−3778.

[4] D. B. J. Easton, D. Leaver, T. J. Rawlings, *J. Chem. Soc., Perkin Trans. 1* **1972**, *1*, 41−45.

[5] H. Junge, H. Musso, U. I. Zahorszky, *Chem. Ber.* **1968**, *101*, 793−800.

[6] [6a] L. Brandsma, P. W. Schuijl, *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 30. [6b] P. W. Schuijl, H. T. J. Bos, L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 597. [6c] K. Praefecke, C. Weichsel, *Liebigs Ann. Chem.* **1980**, 1604−1619. [6d] H. Shimizu, N. Kudo, T. Kataoka, M. Hori, *Tetrahedron Lett.* **1990**, *31*, 115−118.

[7] [7a] T. Bowles, R. Jones, A. E. A. Porter, J. A. Rechka, H. S. Rzepa, D. J. Williams, *J. Chem. Soc., Chem. Commun.* **1985**, 1590−1593. [7b] T. Bowles, R. J. Gillespie, A. E. A. Porter, J. A. Rechka, H. S. Rzepa, *J. Chem. Soc., Perkin Trans. 1* **1988**, 803−812.

[8] Y. Mollier, N. Lozac'h, *Bull. Soc. Chim. Fr.* **1961**, 614−618.

[9] R. Huisgen, X. Li, G. Mloston, C. Fulka, *Eur. J. Org. Chem.* **2000**, 1695−1702.

[10] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, G. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435.

[11] G. M. Sheldrick, *SHELX97, Program for the refinement of Crystal Structures*, Univ. Göttingen, Germany, **1997**.

Received January 27, 2003

