



Photoinduced Molecular Rearrangements. The Photochemistry of 1,2,4-Oxadiazoles in the Presence of Sulphur Nucleophiles. Synthesis of 1,2,4-Thiadiazoles

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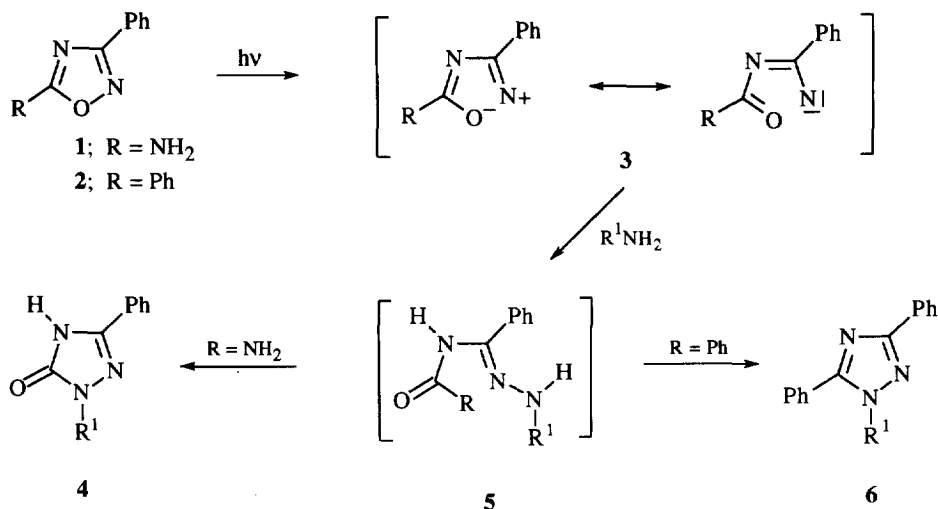
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Abstract: The photochemistry of some 1,2,4-oxadiazoles in the presence of sulphur nucleophiles has been investigated. Irradiation of the 5-amino-3-phenyl- and 3,5-diphenyl-1,2,4-oxadiazole at $\lambda = 254$ nm in methanol in the presence of sodium hydrogen sulphide or thiols gave a photo-induced redox reaction at the ring O-N bond, leading to the corresponding *N*-substituted benzamidines. By contrast, irradiation of the 5-amino-3-phenyl-1,2,4-oxadiazole in the presence of thioureas or thiocarbamates, essentially gave 3-phenyl-5-substituted 1,2,4-thiadiazoles, which presume an N-S bond formation between the ring-photolytic species and the sulphur nucleophile. In turn, irradiation of the same 5-amino-3-phenyl-1,2,4-oxadiazole in the presence of thioamides again afforded the redox reaction; in addition, amounts of 3-phenyl-5-substituted-1,2,4-thiadiazoles were also formed. Some mechanistic considerations are reported, and synthetic methodologies leading to 1,2,4-thiadiazoles are emphasized.
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Introduction

Photoinduced molecular rearrangements of O-N bond-containing five-membered heterocycles can provide interesting methodologies in synthesis of target compounds.^{1,2} In this context, significant examples have been recognised in the photochemistry of 1,2,5- and 1,2,4-oxadiazoles.²⁻⁷ Particularly, for example, studying the photochemistry of 1,2,4-oxadiazoles, we recently reported⁷ the formation of 1,2,4-triazoles **4** or **6** by irradiation of 1,2,4-oxadiazoles **1** or **2**, respectively, in the presence of primary aliphatic amines which act as an *external* nitrogen nucleophile. In the same context, in the irradiation of 3-(*ortho*-aminophenyl)-5-substituted 1,2,4-oxadiazoles, where the *ortho*-aminophenyl moiety act as an *internal* nitrogen nucleophile, concomitant formation of indazoles and benzimidazoles (these latter arising from a carbodiimide intermediate) has been observed.⁷ The first step of these photoreactions has been considered the heterolytic photolysis of the ring O-N bond into **3** (zwitterion or nitrene). The fate of this resulting intermediate will then depend on the presence of a nucleophile (which the photolytic species will capture) and on the possibility of a subsequent heterocyclization reaction. Interestingly, the formation of the N-N bond between the electrophilic nitrogen of **3** and the *external* nitrogen nucleophile leading to intermediates of the type **5** appears of some significance, both from mechanistic and synthetic aspects.



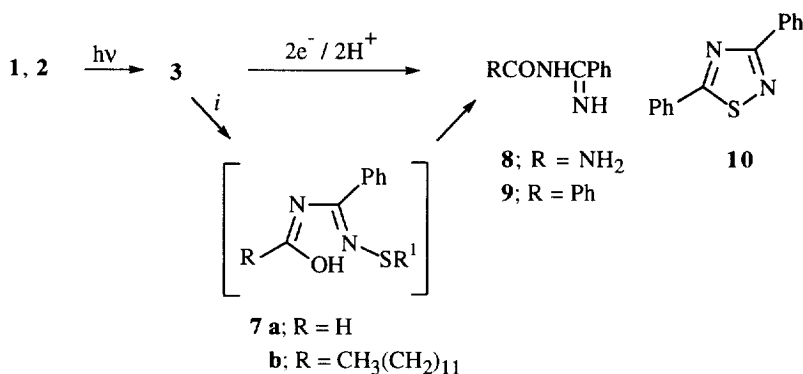
Scheme 1

In pursuing our investigations on these aspects of the photochemistry of O-N bond-containing five-membered heterocycles, and aiming to point out alternative and environmentally-compatible syntheses of heterocycles, we became interested on the photoreactivity of 1,2,4-oxadiazoles when irradiated in the presence of sulphur nucleophiles. An attractiveness of this photoreaction could have been recognised in the possibility of the formation of an N-S bond between the nucleophilic reagent and the electrophilic nitrogen of the photolytic species. In addition, depending on the nature of the reagent, subsequent heterocyclization reactions of resulting intermediates could have appointed new methodologies in heterocyclic synthesis. For the study, we have considered the 5-amino-3-phenyl- (1), and the 3,5-diphenyl-1,2,4-oxadiazole (2) as representative substrates. Significantly, compound 1 is characterised by a marked photoreactivity in one hand, and by the presence of a potential leaving group at C(5), in the other.^{7,8}

Results and Discussion

We have at first considered irradiations of oxadiazoles 1 and 2 at $\lambda = 254$ nm in methanol and in the presence of sodium hydrogen sulphide. The photoreaction (which, as expected, proceeded with lower rate of conversion in the case of compound 2) gave the corresponding *N*-carbamoyl- (8) and *N*-benzoyl-benzamidin (9), respectively. Interestingly, the irradiation of the diphenyloxadiazole 2 showed the formation of trace amounts of the diphenyl-1,2,4-thiadiazole 10, whereas similar thiadiazole ring-closure was not observed in the irradiation of the 5-amino-compound 1. In addition, photolysates also contain elemental sulphur. Since compounds 1 and 2 were unchanged when reacted with sodium hydrogen sulphide under non photochemical conditions, the formation of 8 and 9 may be viewed as a photoinduced redox reaction at the ring O-N bond.

Taking into account the redox properties of hydrogen sulphide or sulphide anion, the photoreaction could imply electrons transfer from the sulphidryl anion to the electrophilic nitrogen of the photolytic species. On the other hand, the formation of the thiadiazole ring **10** would require intermediacy of **7a**, which will be formed either via nucleophilic attack or via electron transfer, proton addition and cross-coupling between the thiyl radical and the nitrogen centered radical. In turn, **7a** may give rise also to the reduction products. Benzamidines **8** and **9**, together with the dodecane-disulphide, were also formed by irradiating oxadiazoles in the presence of dodecane-1-thiol. Again, a direct electron transfer process from the thiol to the photolytic species, or the involvement of the intermediate **7b** can be reasonably invoked.



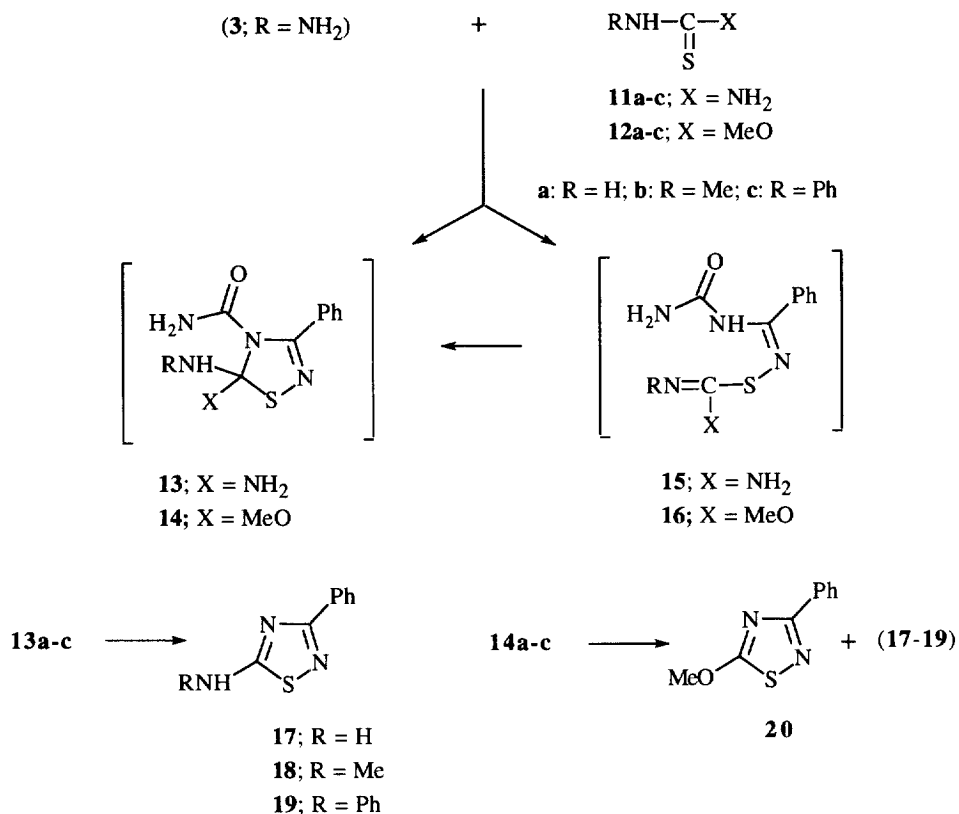
Scheme 2 - Reagents: *i* HS⁻ / H₂O or CH₃(CH₂)₁₁SH

An attractive scheme to show the formation of an N-S bond was to investigate irradiations in the presence of thioureas, confiding in the marked nucleophilic character of the sulphur atom of the C=S moiety. To this study, we irradiated oxadiazoles in the presence of a slight excess of the reagent. Molar ratios 2/1 between thioureas and the substrate turned out better; on the other hand, irradiation tests carried out for the oxadiazole **1** and thiourea showed that higher concentration of the reagent decreased the rate of the photoconversion, likely because of competitive absorption of both the reagent and the oxadiazole at $\lambda = 254$ nm; by contrast, lower concentration of the reagent causes interference by the nucleophilic solvent.⁸

Irradiation of compound **1** in the presence of the thioureas **11a,b** gave the 5-amino-3-phenyl- (**17**) (64%) and the 5-*N*-methylamino-3-phenyl-1,2,4-thiadiazole (**18**) (67%), respectively, whereas few percent (HPLC) of the *N*-carbamoylbenzamidines **8** were formed. Similarly, irradiation of **1** in the presence of *N*-phenylthiourea (**11c**), gave the 5-*N*-phenylamino-3-phenyl-1,2,4-thiadiazole (**19**) (45%), while significant amounts (about 20%) of **8** (and, correspondingly, elemental sulphur and phenylcyanamide) were isolated. Because of the occurrence of thermal and/or photochemical side-reactions (which were discarded), yields of isolated thiadiazoles were not improved. Nevertheless, our opinion is that this procedure could be generalised for an efficient synthesis of 5-amino-3-aryl- or 5-*N*-substituted amino-3-aryl-1,2,4-thiadiazoles, alternative to the non photochemical methodologies.⁹

Rather crude and with much lower significance, however, was the photoreaction of the 3,5-diphenyloxadiazole (**2**) with thiourea. Because of the lower photoreactivity of this substrate,⁷ as well as because

of the occurrence of side-reactions, very low yields of the 5-amino-thiadiazole **17** were isolated, while some other minor photoproducts were also formed, and then this photoreaction was not investigated further.

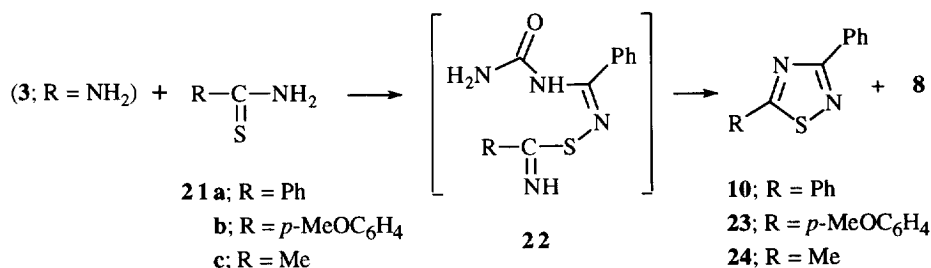


Scheme 3

Taking into account the documented¹⁰ photostability of thiourea and substituted thioureas under irradiation at 254 nm in ethanol, the formation of thiadiazoles **17-19** suggests that sulphur reagents participate in the formation of the final heteroring by the C=S moiety. A reasonable pathway (Scheme 3) assumes a reaction of the photolytic species (**3**; R = NH₂) with the thioureas, and thiadiazolines **13** as key-intermediates. However, if the ring-closure into **13** is a concerted process between **3** and the C=S moiety of the reagent, or a stepwise reaction presumably involving **15**, remains an open question. On the other hand, although we have no evidences about this point, the formation of 1,2,4-thiadiazoles **17-19** from thiadiazolines **13** could be roughly considered a solvent-assisted elimination reaction (thermally- or photo-induced) leading to the aromatic heteroring. In turn, intermediates **15** could also develop into the reduction product **8** to an extent depending on substituent. In regard to this, isolation of phenylcyanamide [arising from (**15**; R = Ph)] in the irradiation of compound **1** in the presence of phenylthiourea fits well in this hypothesis.

To gain information on the role of the sulphur nucleophile in the thiadiazole ring-closure, we have considered irradiations in the presence of thiocarbamates. By these reagent, too, one should have expected the formation of 1,2,4-thiadiazoles. Really, irradiation of **1** in the presence of **12a-c**, besides significant amounts of the *N*-carbamoyl-benzamidine (**8**) (about 20%), gave mixtures of both the 5-methoxythiadiazole **20** in one hand, and the 5-amino-(**17**), 5-*N*-methylamino-(**18**), or 5-*N*-phenylamino-thiadiazole (**19**), respectively, in the other. The competitive elimination from the presumed thiadiazoline intermediates **14** appeared largely depending on substituent: in a typical experiment, irradiation in the presence of **12a** gave **20** (42%) and **17** (11%), while irradiation in the presence of **12b** gave the methylamino compound **18** (37%), but only few percent of the 5-methoxy-thiadiazole **20**. Furthermore, irradiation in the presence of **12c** again gave **20** (25%) and **19** (25%). Therefore, a rather intriguing process, likely involving a photolytic step, should be argued to explain the formation of heteroaromatic thiadiazoles from the presumed thiadiazolines **14** (or **13**, too).

Finally, we have considered irradiations in the presence of thioamides. Surprisingly, irradiation of **1** in the presence of arylthioamides **21a,b** essentially gave the *N*-carbamoylbenzamidine **8** (60%), while thiadiazoles **10** and **23**, respectively, were isolated in about 15% yields. Significantly, photolysates also contain elemental sulphur and aryl nitriles, which should arise from (**22**; R = Ph, *p*-MeOC₆H₄) undergoing the reduction. Similarly, irradiation of **1** in the presence of thioacetamide also gave **8** (70%), but only few percent of the corresponding 5-methyl-3-phenyl-1,2,4-thiadiazole (**24**). Since literature¹¹ reports that prolonged irradiations of thioamides at 254 nm in ethanol produces hydrogen sulphide and nitriles, a first-glance hypothesis to explain our results could have considered the hydrogen sulphide thus formed as the ring-reducing reagent. However, parallel experiments allowed us to exclude this. Therefore, although the usual electron transfer process from the sulphur reagent to the ring-photolytic species can not be excluded, our opinion is that photoreactions in the presence of thioamides should involve intermediates **22**, which will develop both into the redox reaction (essentially) and into the heterocyclization reaction (poorly). By contrast, when intermediates **15** or **16** are considered, *internal* conjugation in the amidine-type moiety (or iminoether-type, respectively) linked at the sulphur atom, could suppress to some extent the relevance of the reduction process; thus, the heterocyclization will prevail. On the other hand, the different (and competing) redox and nucleophilic properties of thioamides in one hand and of thioureas (or thiocarbamates) in the other could also play a significant role in the course of the photoreactions. At the moment, it is not possible to specify which way is operating. Determination of the reduction potentials for compounds **1** and **2**, as well as the oxidation potentials of some of the thioderivatives used in this paper should allow a better understanding of this point.



Scheme 4

As a conclusive comment, the whole results show that photolytic species arising from the 1,2,4-oxadiazole ring do react with sulphur reagents by forming an N-S bond. In turn, the final products will depend on the structure of the resulting intermediate. In our case, both the photoreduction and the formation of 1,2,4-thiadiazoles appear of some significance in synthetic projects. However, the particular structure of the irradiated substrate appears a determining factor both in the photoreactivity and in the development into final products. In this connection, in addition to poor results observed in the irradiation of the diphenyloxadiazole **2** in the presence of thiourea, it is to be also noted that attempts to realize similar photoinduced transformation into the thiadiazole ring by irradiating the 5-amino-3-methyl-1,2,4-oxadiazole¹² in the presence of thiourea were unsuccessful; starting material was recovered in this case, and this is probably because of the low and unproductive absorbance of this oxadiazole derivative at the wavelength used.

Experimental Section

Materials and Methods. For instruments and general procedures see our previous papers. HPLC analyses were performed by using a C-18 SIL-X-10 Perkin-Elmer column. Flash chromatography¹³ was performed by using ethyl acetate or mixtures of light petroleum (fraction boiling in the range of 40-60°C) and ethyl acetate in varying ratios. Anhydrous methanol, dodecane-1-thiol, thiourea (**11a**), *N*-methylthiourea (**11b**), *N*-phenylthiourea (**11c**), thiobenzamide (**21a**) and thioacetamide (**21c**) were obtained from Aldrich Chemical Co. and were used without purification, except **11c** which was purified by chromatography. Standard (0.2 M) solution of sodium hydrogen sulphide in methanol was freshly prepared.¹⁴ Thiocarbamates **12a**,^{15,16} **12b**¹⁶ and **12c**¹⁷ were prepared as reported. The *p*-methoxythiobenzamide (**21b**) was prepared by sulphuration¹⁸ of the *p*-methoxybenzamide (Aldrich) with Lawesson reagent (Aldrich) in refluxing benzene, m.p. 145-148°C (from benzene-light petroleum) [lit.,¹⁹ m.p. 149°C].

Oxadiazoles **1**¹² and **2**²⁰ were prepared as reported. Photochemical reactions were carried out in anhydrous methanol by using a Rayonet RPR-100 photoreactor fitted with 16 lamps irradiating at $\lambda = 254$ nm (in quartz vessels) and a merry-go-round apparatus. When the case, photoproducts were compared with authentic samples.

Irradiations in the Presence of Sodium Hydrogen Sulphide and Thiols. - To a sample of the oxadiazole **1** (0.5 g; 3.1 mmol) or **2** (0.5 g; 2.2 mmol) in methanol (40 or 55 ml, respectively) was added an excess of the freshly prepared 0.2 M sodium hydrogen sulphide in methanol (60 or 45 ml, respectively). The solution was apportioned into two quartz tubes and then irradiated for the time indicated. After removal of the solvent, the residue was chromatographed. Elemental sulphur was discarded.

Irradiation (2 h) of the oxadiazole **1**, besides starting material (0.1 g; 20%), gave the *N*-carbamoylbenzamidine (**8**) (0.30 g; 60%), m.p. 134 °C (from benzene-ethyl acetate) [lit.,²¹ m.p.135-136°C].

Similarly, irradiation (4 h) of the oxadiazole **2** returned starting material (0.15 g; 30%) and gave the *N*-benzoylbenzamidine (**9**) (0.2 g; 40%), m.p. 100-102 °C (from hexane) [lit.,²² m.p. 98-100 °C]. HPLC and GC-MS analysis of enriched fractions revealed the presence of trace amounts of the 3,5-diphenyl-1,2,4-thiadiazole (**10**).²³

A solution of the oxadiazole **1** (0.05 g; 0.31 mmol) in methanol (10 ml) containing an excess of 1-dodecanethiol (0.2 g; 1.0 mmol) was irradiated for 30 minutes. HPLC analysis of the photolysate gave **1** (40%) and **8** (60%). The dodecane-disulphide separated was compared with a sample obtained by oxidation of the thiol with iodine in methanol.

Similarly, after irradiating the oxadiazole **2** (0.05 g; 0.22 mmol) in methanol (10 ml) containing an excess of 1-dodecanethiol (0.16 g; 0.8 mmol) for 60 minutes, HPLC analysis gave **2** (80%) and **9** (20%).

Irradiations in the Presence of Thioureas, Thiocarbamates and Thioamides- To a sample of compound **1** (0.5 g; 3.1 mmol) in methanol (100 ml) was added a slight excess of the appropriate thiourea (**11a-c**), thiocarbamate (**12a-c**) or thioamide (**21a-c**) (6.2 mmol). The solution was apportioned into two quartz tubes and then irradiated for 2.5 h. After removal of the solvent, chromatography of the residue returned starting material (about 20%), and gave variable amounts of elemental sulphur (to an extent roughly corresponding to the reduction product) and, in some case, amounts of solvolytic photoproducts⁸ (discarded).

Irradiation in the presence of **11a** gave the 5-amino-3-phenyl-1,2,4-thiadiazole (**17**) (0.35 g; 64%), m.p. 154 °C (from ethanol), [lit.,²⁴ m.p. 155 °C] and few percent (by HPLC) of **8**.

Irradiation in the presence of **11b** gave the 5-*N*-methylamino-3-phenyl-1,2,4-thiadiazole **18** (0.40 g; 67%), m.p. 155 °C (from ethanol), [lit.,²⁵ m.p. 155-157 °C] and few percent (by HPLC) of **8**.

Irradiation in the presence of **11c** gave the 5-*N*-phenylamino-3-phenyl-1,2,4-thiadiazole (**19**) (0.35 g; 45%), m.p. 172 °C [lit.,²⁵ m.p. 173-174 °C], phenylcyanamide (0.07 g; 20%), m.p. 40-45 °C [lit.¹⁰ m.p. 45-47 °C] and **8** (0.1 g; 20%).

Irradiation in the presence of **12a** gave the 5-methoxy-3-phenyl-1,2,4-thiadiazole (**20**) (0.25 g; 42%), m.p. 32 °C [lit.,²⁶ m.p. 32 °C], **17** (0.06 g; 11%), and **8** (0.1 g; 20%).

Irradiation in the presence of **12b** gave few amounts of **20** (about 5%), **18** (0.22 g; 37%) and **8** (0.1 g; 20%).

Irradiation in the presence of **12c** gave **20** (0.15 g; 25%), **19** (0.2 g; 25%), and **8** (0.1; 20%)

Irradiation in the presence of thiobenzamide (**21a**), besides benzonitrile, gave the 3,5-diphenyl-1,2,4-thiadiazole (**10**) (0.11 g; 15%), m.p. 88-90 °C [lit.,²³ m.p. 90 °C] and **8** (0.30 g; 60%).

Similarly, irradiation in the presence of *p*-methoxy-thiobenzamide (**21b**), besides the *p*-methoxy-benzonitrile (0.25 g; 60%), gave the 3-phenyl-5-*p*-methoxyphenyl-1,2,4-thiadiazole (**23**) (0.12 g; 15%), and then compound **8** (0.3 g; 60%). Compound **23** had m.p. 100 °C (from light petroleum). Anal. Calcd. for C₁₅H₁₂N₂OS: C (67.14); H (4.51); N (10.44). Found: C (67.10); H (4.40); N (10.60). ¹H-NMR (CDCl₃) (δ ppm): 3.90 (3H, s), 7.0-8.4 (9H, m). MS m/z 268 (M⁺).

Irradiation in the presence of thioacetamide (**21c**), gave few percent of the 5-methyl-3-phenyl-1,2,4-thiadiazole (**24**), oil, [lit.,²⁷ m.p. 14 °C], and then compound **8** (0.35 g; 70%).

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