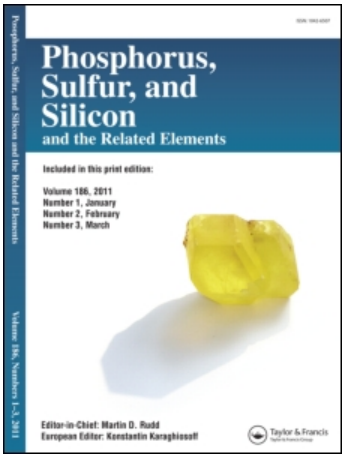

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Synthesis of Thiadiazine and Triazino[3,4-*b*]thiadiazine Derivatives

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*The addition of dimethyl acetylenedicarboxylate (DMAD) to dithizon afforded dimethyl-trans- 5,6-dihydro-4-phenyl-2-phenylhydrazino-1,3,4-thiadiazin-5,6-dicarboxylate (**2**) and dimethyl-2-methoxycarbonylmethylene-4,8-diphenyl-1,2,4-triazino[3,4-b]-1,3,4-thiadiazin-3-one-6,7-dicarboxylate (**3**).*

Keywords Dimethyl acetylenedicarboxylate (DMAD); dithizon; thiadiazine; triazino[3,4-*b*] thiadiazine

INTRODUCTION

Thiadiazine derivatives are widely used as nematicides, fungicides, herbicides and insecticides.[1] Some thiadiazine derivatives have activity against tripanosoma cruzi amastigotes.[2]

1,2,4-Triazines are an important class of compounds, which act as antimicrobial,[3] antiviral,[4] anti-inflammatory,[5–7] and antimalarial[8] agents. Some of them are used as antibacterials[9–11] and antidiabetics.[12] 3-Sulfanilamido-5-dimethylethyl-1,2,4-triazine is manufactured and used as a drug.[13] 6-Azacytidine derivatives show antiviral effects on the adenovirus genome,[14] whereas some triazinone derivatives are used as antiulcer agents.[15] Fluorene containing substituted 3-thioxo-1,2,4-triazin-5-ones exhibit antihuman immune virus activity.[16] A series of

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basically substituted 1,3,4-thiadiazines were synthesized. Several synthetic methods were used to prepare thiadiazines: *i*) treatment of a 2-(β-hydroxyalkyl)carboxylic acid hydrazide with P_4S_{10}[17]; *ii*) cyclodehydration of a 2-(β-hydroxyalkyl)thio carboxylic acid hydrazide by concentrated H_2SO_4[18]; *iii*) condensation of a β-hydrazinoalkyl thiol with nitriles, imino esters, aldehydes or cyanogen bromide[19]; and *iv*) cyclization of thiobenzoylhydrazones and mercaptoacetylhydrazones to derivatives of 1,3,4-thiadiazoline and 1,3,4-thiadiazin-5-one, respectively.[20–22] Many fused rings based on the 1,3,4-thiadiazine nucleus have been synthesized to evaluate their biological activities.[23–27]

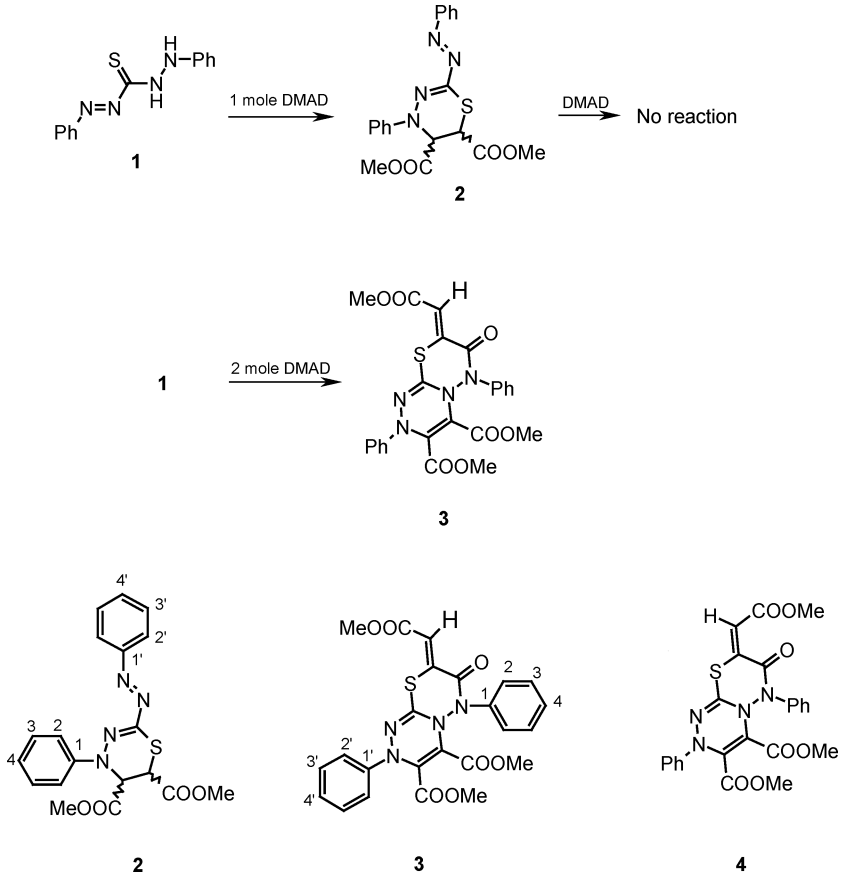
In continuation of our work on the synthesis of heterocyclic systems containing nitrogen and sulfur,[28] we describe here the synthesis of new thiadiazine and triazino[3,4-*b*]thiadiazine derivatives.

RESULTS AND DISCUSSION

Reaction of DMAD with dithizon (1:1) in methanol results in the formation of a single compound which was identified as dimethyl-*trans*-5,6-dihydro-4-phenyl-2-phenyl-hydrazino-1,3,4-thiadiazin-5,6-dicarboxyla te (**2**). Compound **2** contains two centers of chirality and two diastereomers are possible but TLC and the NMR spectra of this compound show the presence of only one species. Its ^{1}H NMR spectrum exhibits signals corresponding to two C-H groups at δ 4.66 (d, $J = 2.9$ Hz) and 5.56 (d, $J = 2.9$ Hz). In this compound, for a pair of isomers $^3J_{cis}$ is larger than $^3J_{trans}$. This unusual result most probably arises from an effect of the electronegative groups.[29–31] These data indicated that two Michael type additions have occurred to afford dimethyl-*trans*-5,6-dihydro-4-phenyl-2-phenylhydrazino-1,3,4-thiadiazin-5,6-dicarboxylate**2**. All attempts for cyclization of compound **2** with DMAD were unsuccessful.

DMAD was reacted with dithizon (2:1) in methanol. Two heterocyclic compounds can be expected from this reaction. They are **3** or the isomer **4**. For these compounds two orientations of the substituents H and CO_2Me at the exocyclic C=C double bond are possible; however TLC and the NMR spectra of this compound indicated the presence of only one species. Its ^{1}H NMR spectra showed the signal of the exo-methylene proton as singlet at $\delta = 5.97$ ppm. If the reaction product was **4** one would expect the exo-methylene proton to be more shielded than exo-methylene proton in structure **3**.[32] This deshielding has its origin in the magnetic anisotropy of carbonyl group (N–C=O). The dimethyl-2-methoxycarbonylmethylene-4,8-diphenyl-1,2,4-triazino[3,4-*b*]-1,3,4-thiadiazin-3-one-6,7-dicarboxylate structure (**3**) was assigned based on NMR, MS, and IR data as well as elemental

analysis. These data indicated that a Michael type addition,[32c] and a Diels-Alder [4+2] cycloaddition reaction have occurred to afford this compound (Scheme 1).



SCHEME 1

In conclusion, we can assume that in the reaction of dithizon with DMAD, sulfur and nitrogen nucleophiles add to the activated triple bond by Michael type addition and Diels-Alder [4+2] cycloaddition reaction to give **2** and the fused heterocyclic compound **3**. The main advantages of these reactions are mild reaction conditions, high yields and a one-pot synthesis. The compounds reported could show interesting biological properties.[1–16]

EXPERIMENTAL

The melting points were obtained using an Electrothermal IA 9100 Digital melting point apparatus. The IR spectra were recorded on a Bruker IFS-88 instrument (CsI disks for the range 4000–500 cm^{-1}). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer (^{1}H, 300.134 MHz; ^{13}C, 75.469 MHz) using TMS as internal standard. Mass spectrometric measurements were made on an Agilent Technologies 6890 N Network GC system.

Dimethyl-*trans*-5,6-dihydro-4-phenyl-2-phenylhydrazino-1,3,4-thiadiazin-5,6-dicarboxylate (2)

A solution of dithizon (1 mmol) and DMAD (1 mmol) in 15 mL of MeOH was heated at reflux for 3 h. The solution was cooled and the reaction vessel set aside overnight. The crystals that formed were separated. Yield 82%, m.p. 123–124°C; MS: *m/z* 398 (M^+); FT-IR: CO 1737 cm^{-1};^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.66 (d, J = 2.9 Hz, 1H, CH), 5.56 (d,J = 2.9 Hz, 1H, CH), 7.14 (m, 10H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 37.9 (CH), 39.6 (CH), 53.0 (OMe), 56.2 (OMe), 122.4 (C-2), 123.2 (C-4), 123.5 (C-2'), 128.0 (C-3), 130.3 (C-3'), 130.9 (C-4'), 143.4 (C-1), 145.5 (C-1'), 150.3 (C=N), 167.8 (CO_2), 166.3 (CO_2). Anal. Calcd. for $C_{19}H_{18}N_4O_4S$: C, 57.27; H, 4.55; N, 14.06. Found: C, 57.18; H, 4.54; N, 14.03.

Dimethyl-2-Methoxycarbonylmethylene-4,8-diphenyl-1,2,4-triazino[3,4-*b*]-1,3,4-thiadiazin-3-one-6,7-dicarboxylate (3)

A solution of dithizon (1 mmol) and DMAD (2 mmol) in 15 mL of MeOH was heated at reflux for 4 h. The solution was cooled and the reaction vessel set aside overnight. The crystals that formed were separated. Yield 92%, m.p. 156–157°C; MS: *m/z* 508 (M^+); FT-IR: CO 1749, 1694 cm^{-1};^{1}H NMR (DMSO-d_6): δ 3.34 (s, 3H, OMe), 3.36 (s, 3H, OMe), 3.38 (s, 3H, OMe), 5.97 (s, 1H, C=CH), 7.20 (m, 10H, Ar-H);^{13}C NMR (DMSO-d_6): δ 49.6 (OMe), 51.3 (OMe), 52.3 (OMe), 91.2 (CH=C), 123.5 (C-2), 125.9 (C-2'), 127.9 (C-4), 128.9 (C-4'), 129.6 (C-3), 129.7 (C-3'), 136.9 (C-1), 139.1 (C-1'), 149.6 (C=CH), 153.8 (C=C), 154.7 (C=C), 157.0 (C=N), 161.3 (C=O), 163.4 (CO_2), 164.6 (CO_2), 167.4 (CO_2). Anal. Calcd. for $C_{24}H_{20}N_4O_7S$: C, 56.69; H, 3.96; N, 11.02. Found: C, 56.66; H, 3.91; N, 11.09.

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