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SYNTHESIS OF 1,2,4-TRIAZIN-5-ONES THROUGH [4+2] CYCLOADDITION OF 1,2,4-TRIAZA-1,3-DIENES WITH DIPHENYLKETENE

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Abstract – On heating 1,2,4-triaza-1,3-dienes **1** with diphenylketene, [4+2] cycloaddition took place smoothly to afford the corresponding 1,2,4-triazin-5-one derivatives **2** in good yield.

INTRODUCTION

Aza-Diels-Alder reaction provides one of the most useful methods for constructing a variety of six-membered heterocyclic systems containing one or more nitrogen atoms, which are important components of biologically active compounds.[1] Particularly, a 1,2,4-triazin-5-one ring-system, including the selective phosphodiesterase type 5 inhibitor vardenafil for the treatment of male erectile dysfunction,[2] is of interest in view of its biological activities.[3] Although a [4+2] cycloaddition of 1,2,4-triaza-1,3-dienes with ketenes would directly produce 1,2,4-triazin-5-ones, to the best of our knowledge there are no reports on this type of reaction.[4] Moreover, it is difficult to predict the formation of either 1,2,4-triazin-5-one or 1,2,4-triazin-6-one (Scheme 1). From our studies on hetero-Diels-Alder reactions,[5] we have reported several types of cycloadditions of ketenes with 1-aza-,[6] 1,3-diaza-[7] and 1,4-diaza-1,3-dienes[8] (Scheme 2). This paper describes the first example of a [4+2] cycloaddition of 1,2,4-triaza-1,3-dienes with diphenylketene, resulting in the regioselective construction of a 1,2,4-triazin-5-one ring-system.

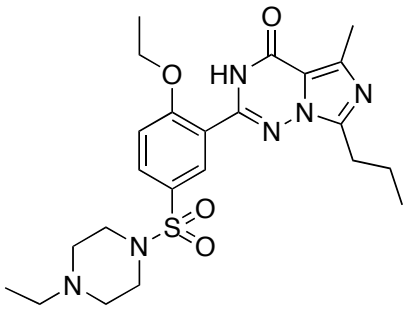
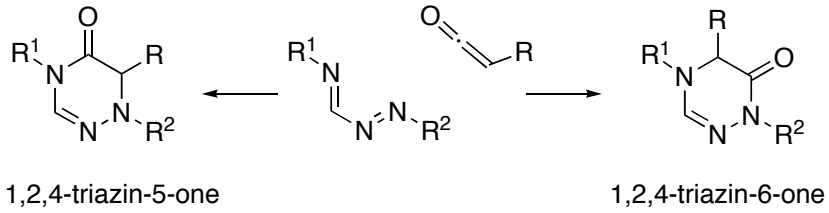
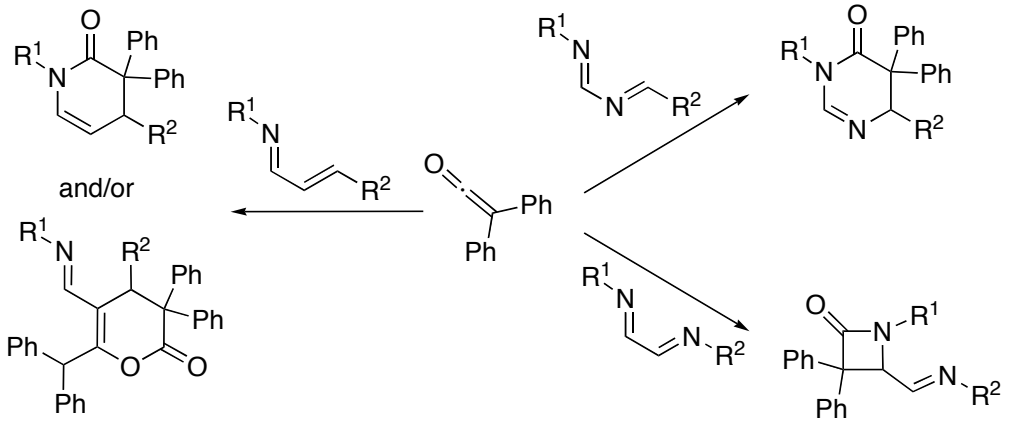


Figure 1. Vardenafil



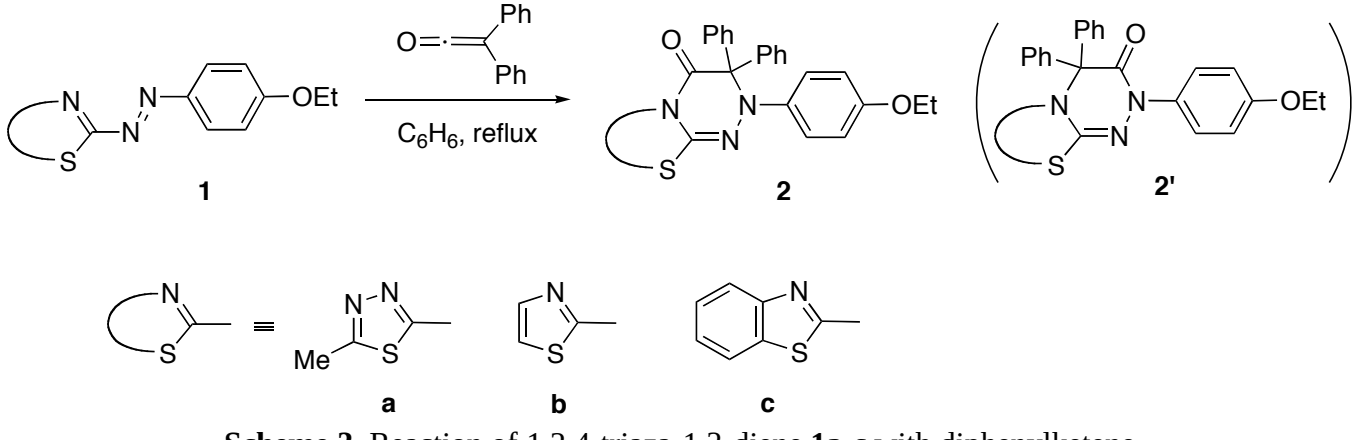
Scheme 1. Possible products in a reaction of 1,2,4-triaza-1,3-butadiene with ketene



Scheme 2. Reactions of some azadienes with diphenylketene

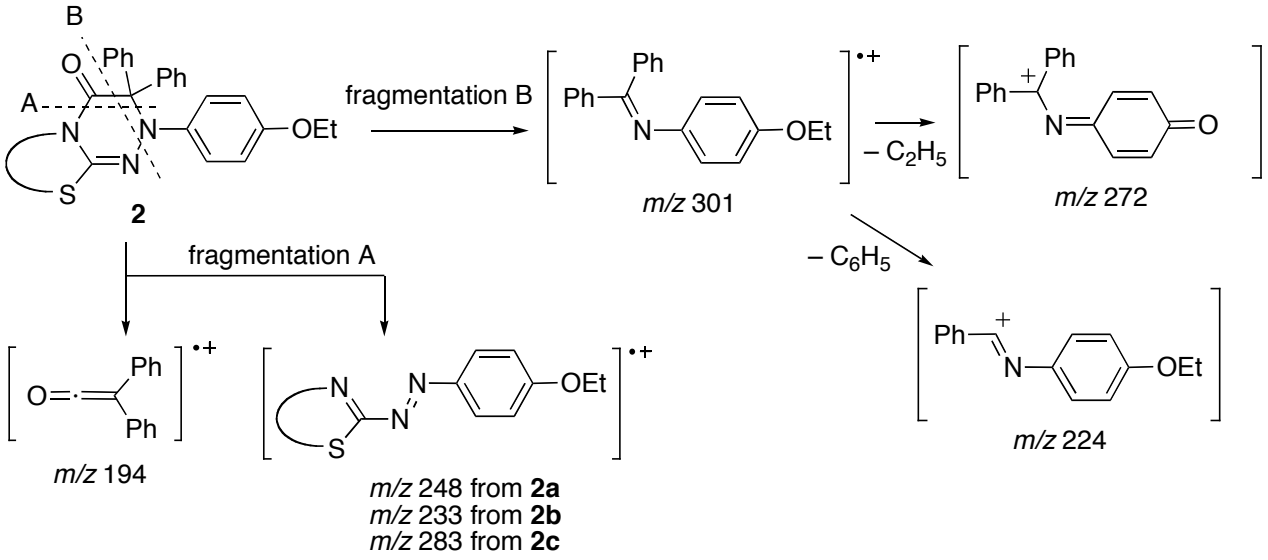
RESULTS AND DISCUSSION

The 1,2,4-triaza-1,3-dienes **1** were readily prepared by diazo coupling between ethoxybenzene and diazonium compounds derived from the corresponding amines, which were commercially available, according to the reported method.[9] When 1,2,4-triaza-1,3-diene, (1,3,4-thiadiazo-2-lyl)azobenzene **1a** was treated with diphenylketene in dry benzene under reflux conditions for 24 h, the [4+2] cycloaddition product **2a** was obtained in 79% yield. The structure was assigned on the basis of analytical and spectral data. The infrared spectrum showed absorptions at 1716 cm^{-1} (C=O). The ^{13}C NMR spectrum indicated signals of an amide carbonyl (δ 160.4 ppm) and quaternary carbon center (δ 75.2 ppm). The parent peak



Scheme 3. Reaction of 1,2,4-triaza-1,3-diene **1a-c** with diphenylketene

ion in the mass spectrum appeared at *m*/*e* 442, showing a 1:1 adduct. Mass fragmentation analysis (Scheme 4 and Table 1) can rule out the regioisomer **2a'** to elucidate **2a**. As well as the fragmentation pattern A as a retro-[4+2] cycloaddition, the peaks caused by fragmentation B were observed at *m*/*z* 301, 272 and 224. Ultimately the structure of **2a** was determined by X-ray crystal-structure analysis (Figure 2).



Scheme 4. Mass fragmentation pattern of **2**

Table 1. Components of the main ions in the mass spectra of **2**

Fragmentation	Elemental composition	Calculated (*m/z*)	Found (*m/z*)		
			2a	**2b**	**2c**
M^+	$C_{29}H_{23}N_3O_2S$	477.1511	-	-	477.1533
M^+	$C_{25}H_{22}N_4O_2S$	442.1462	442.1440	-	-
M^+	$C_{25}H_{21}N_3O_2S$	427.1355	-	427.1360	-
B	$C_{21}H_{19}NO$	301.1466	301.1466	301.1432	*[a)]
A	$C_{15}H_{13}N_3OS$	283.0779	-	-	283.0790
B	$C_{19}H_{14}NO$	272.1074	272.1063	272.1045	272.1099
A	$C_{11}H_{12}N_4OS$	248.0732	248.0734	-	-
A	$C_{11}H_{11}N_3OS$	233.0627	-	233.0615	-
B	$C_{15}H_{14}NO$	224.1074	224.1054	224.1069	224.1054
B	$C_{14}H_{10}O$	194.0730	194.0719	194.0738	194.0730

a) No peak observed.

Similar reactions of (1,3-thiazol-2-yl)- **1b** and (1,3-benzothiazol-2-yl)-azobenzene **1c** with diphenylketene proceeded with [4+2] cycloaddition to give the corresponding 1,2,4-triazin-5-ones **2b** and **2c** in 78% and 72% yields, respectively. These structures were confirmed by comparing with the mass fragmentation patterns of **1a**, **1b** and **1c** (Table 1), all of which demonstrated the same fragmentation peaks causing fragmentation B.

In summary, we demonstrated the first example of the [4+2] cycloaddition of 1,2,4-triaza-1,3-dienes **1** with diphenylketene to provide 1,2,4-triazin-5-one derivatives **2** in good yields.

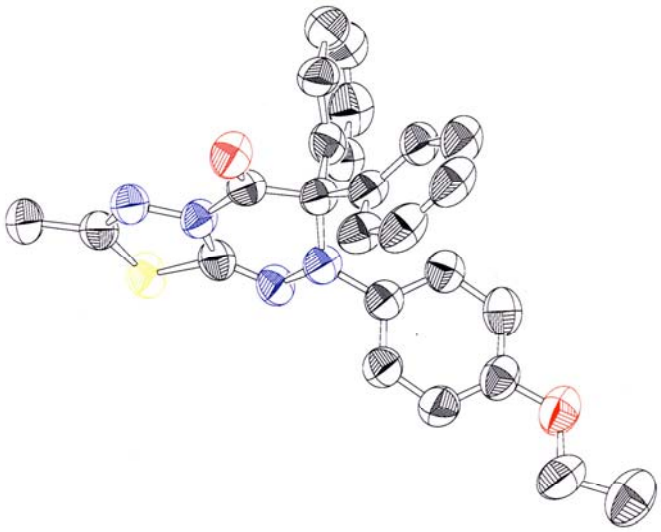


Figure 2. X-Ray crystal structure analysis of **2a**

EXPERIMENTAL

All mps were measured on a Yanagimoto micromelting point apparatus, and are uncorrected. IR spectra were recorded with a Hitachi 270-30 spectrophotometer. NMR spectra were determined using a JEOL JNM-GX 270 spectrometer with tetramethylsilane as an internal standard. *J*-Values are given in Hz. Mass spectra were obtained using a JEOL JMS 700 instrument with a direct system. Column chromatography was carried out on silica gel (Merck, 400 mesh). 1,2,4-Triaza-1,3-dienes **1a**-**1c** were prepared according to the reported procedures.[9]

2-(4-Ethoxyphenyl)-2,3-dihydro-7-methyl-3,3-diphenyl[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-one (2a)

A solution of **1a** (248 mg, 1 mmol) and diphenylketene (320 mg, 1.65 mmol) was heated under reflux for 24 h in dry benzene (20 mL) under N_2. The reaction mixture was condensed *in vacuo* to give a residue. The residue was purified by column chromatography on silica gel with *n*-hexane-AcOEt (10 : 1) to afford **2c** (350 mg, 79%). Mp 168-170 ºC (ligroin); IR (KBr): 1716, 1622, 1582, 1508, 1478, 1450, 1322, 1248, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.30 (3H, t, *J* = 7.0 Hz), 2.35 (3H, s), 3.85 (2H, q, *J* = 7.0 Hz), 6.50 (2H, d, *J* = 8.9 Hz), 6.82 (2H, d, *J* = 8.9 Hz), 7.27-7.33 (6H, m), 7.38-7.42 (4H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz,) δ 160.4, 155.1, 154.2, 139.5, 139.2, 135.5 (2), 129.8 (4), 128.6 (2), 128.2 (4), 125.2 (2), 111.3 (2), 75.2, 63.4, 17.2, 14.8; *Anal.* Calcd for $C_{25}H_{22}N_4O_2S$: C, 67.85; H, 5.01; N, 12.66. Found: C, 67.93; H, 5.19; N, 12.70.

2-(4-Ethoxyphenyl)-2,3-dihydro-3,3-diphenylthiazolo[2,3-*c*][1,2,4]triazin-4-one (2b)

A solution of **1b** (116.5 mg, 0.5 mmol) and diphenylketene (160 mg, 0.82 mmol) was heated at reflux for 9 h in dry benzene (20 mL) under N_2. After concentrating the reaction mixture, the residue was purified column chromatography on silica gel with *n*-hexane-AcOEt (10 : 1) to afford **2b** (166 mg, 78%). Mp 182-185 ºC (MeOH); IR (KBr): 1694, 1614, 1580, 1504, 1478, 1450, 1354, 1274, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.29 (3H, t, *J* = 6.9 Hz), 3.85 (2H, q, *J* = 6.9 Hz), 6.04 (1H, d, *J* = 4.6 Hz), 6.50 (2H, d, *J* = 9.0 Hz), 6.84 (2H, d, *J* = 9.0 Hz), 7.04 (1H, d, *J* = 4.6 Hz), 7.24-7.30 (6H, m), 7.37-7.41 (4H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz,) δ 162.3, 154.8, 139.7, 139.6, 135.7 (2), 129.7 (4), 128.5 (2), 128.2 (4), 124.9 (2), 120.2, 113.4 (2), 107.1, 73.9, 63.4, 14.8; *Anal*. Calcd for $C_{25}H_{21}N_3O_2S$: C, 70.24; H, 4.95; N, 9.83. Found: C, 70.20; H, 5.04; N, 9.97.

2-(4-Ethoxyphenyl)-2,3-dihydro-3,3-diphenylbenzothiazolo[2,3-*c*][1,2,4]triazin-4-one (2c)

A solution of **1c** (283 mg, 1 mmol) and diphenylketene (320 mg, 1.65 mmol) was heated under reflux for 20 h in dry benzene (20 mL) under N_2. The reaction mixture was condensed *in vacuo* to give a residue. The residue was purified by column chromatography on silica gel with *n*-hexane-AcOEt (10:1) to afford **2c** (344 mg, 72%). Mp 161-163 ºC (EtOH); IR (KBr): 1707, 1630, 1582, 1506, 1339, 1281, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30 (3H, t, *J* =7.0 Hz), 3.87 (2H, q, *J* = 7.0 Hz), 6.54 (2H, d, *J* = 9.2 Hz), 6.86 (2H, dt, *J* = 9.2 Hz), 7.16 (1H, td, *J* = 6.4, 1.5 Hz), 7.21 (1H, td, *J* = 6.4, 1.5 Hz), 7.25 (1H, dd, *J* = 7.9, 1.5 Hz), 7.28-7.31 (6H, m), 7.40-7.43 (4H, m), 8.30 (1H, dd, *J* = 7.9, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 125.65 MHz) δ 163.6, 154.8, 139.5, 137.7, 136.0, 135.7 (2), 129.7 (4), 128.5 (2), 128.2 (4), 126.1, 126.0, 124.6 (2), 124.5, 121.8, 116.9, 113.5 (2), 75.0, 63.4, 14.8; *Anal*. Calcd for $C_{29}H_{23}N_3O_2S$: C, 72.94; H, 4.86; N, 8.80. Found: C, 73.09; H, 4.94; N, 8.86.

X-Ray structure analysis of compound 2a

Crystal data: $C_{25}H_{22}N_4O_2S$, M = 442.53, *T* = 298 K, Monoclinic, *a* = 23.432(8) Å, *b* = 12.908(6) Å, *c* = 16.132(3) Å, β = 110.23(2)°, *V* = 4578 (2) $Å^3$ (from setting angles of 25 centered reflections with 33.74 < 2θ < 34.88; λ = 1.54178 Å), space group $P2_1/c$ (#14), *Z* = 8, D_{cal} = 1.284 g cm^{-3}, 0.70 x 0.50 x 0.30 mm, μ(Cu-Kα) = 14.91 cm^{-1}.

Data collection and processing: Rigaku AFC7R four-circle diffractometer with fine-focused 8.3 kW rotating anode generator, ω/2θ scans with ω scan width (1.89 + 0.30 tan θ)°, graphite monochromated Cu-Kα radiation; 8956 reflections measured to $2\theta_{max}$ = 136.2, giving 8736 with $I > 3\sigma(I)$, which were retained in all calculations. No decay correction was observed and no corrections were applied for absorption.

Structure solution and refinement: The structure was solved by direct methods using SIR92 and expanded using Fourier techniques DIRDIF94 and refined by the full matrix least-squares method with all non-H atoms anisotropic. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. The weighting scheme $w = 1/\sigma^2(Fo)$ gave satisfactory agreement analyses. The final R-value was 0.062, $R_w = 0.101$. The maximum and minimum peaks on the final ΔF map corresponded to 0.36 and -0.27 $e^-/Å^3$, respectively.

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