HETEROCYCLES, Vol. 79, 2009, pp. 627 - 633. © The Japan Institute of Heterocyclic Chemistry
Received, 24th September, 2008, Accepted, 10th November, 2008, Published online, 13th November, 2008.
DOI: 10.3987/COM-08-S(D)28

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.

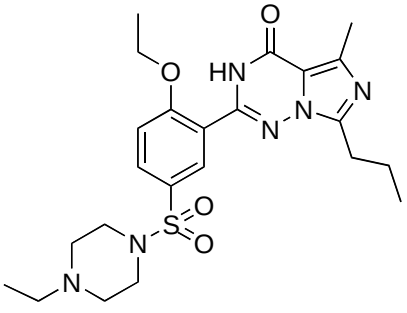
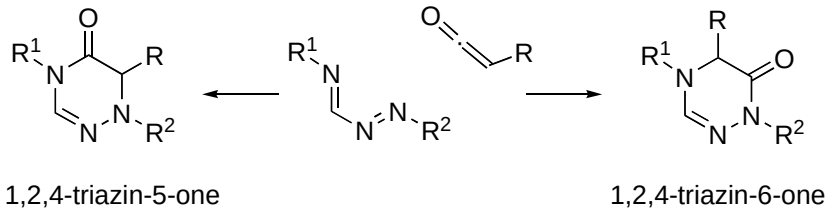
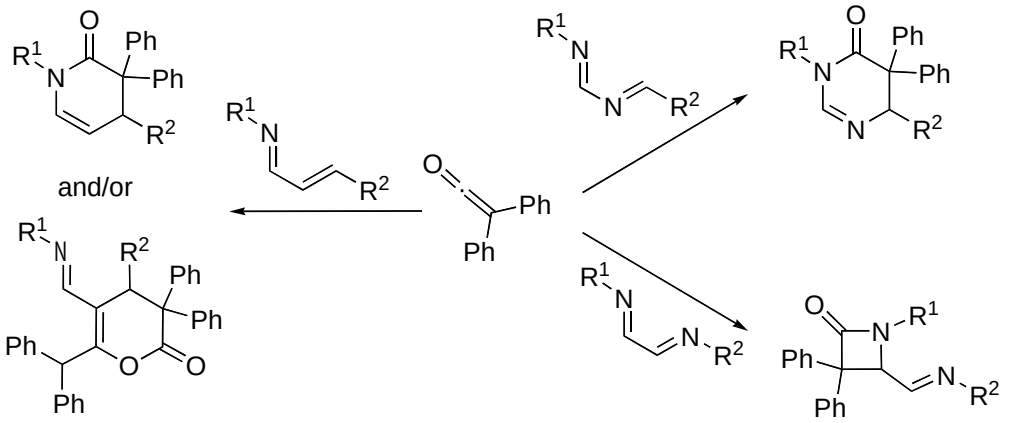


Figure 1. Vardenafil



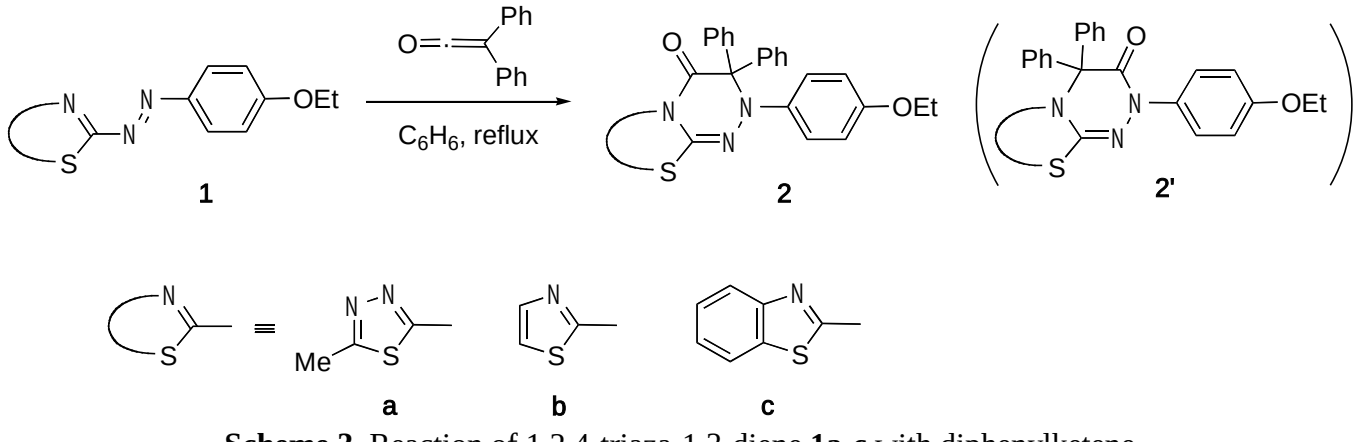
Scheme 1. Possible products in a reaction of 1,2,4-triaza-1,3-butadiene with ketene



Scheme 2. Reactions of some azadienes with diphenylketene

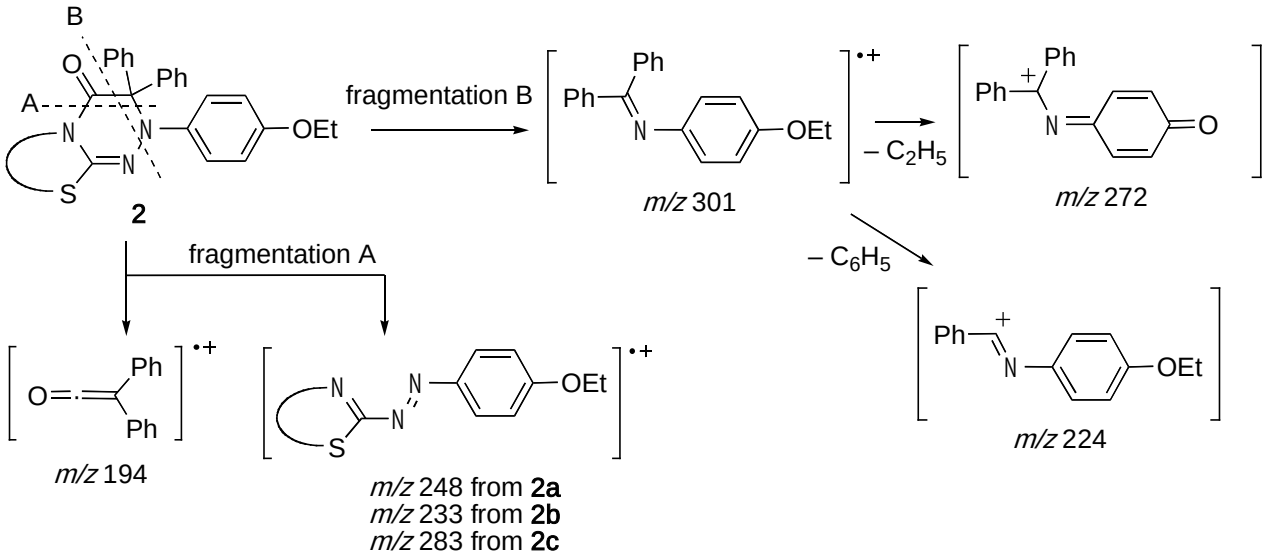
RESULTS AND DISCUSSION

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.

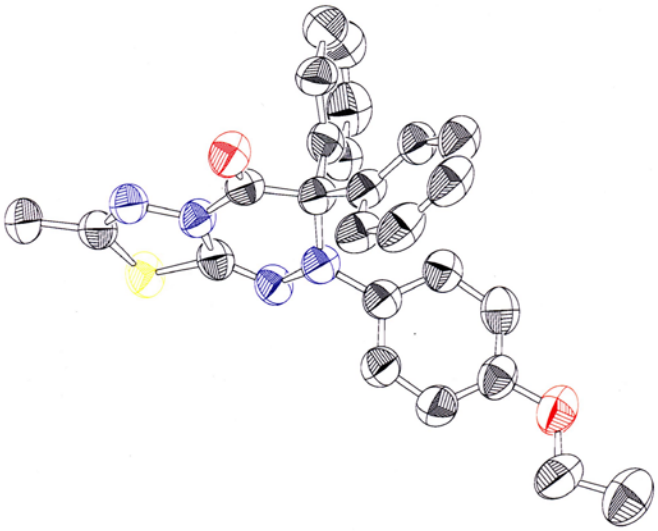


Figure 2. X-Ray crystal structure analysis of **2a**

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 < 2*θ* < 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/2*θ* 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.

ACKNOWLEDGEMENTS

We thank Dr. A. Katoh (Niigata University of Pharmacy and Applied Life Sciences) for his advice on mass fragmentation analysis. We are grateful to N. Eguchi, K. Satoh, and T. Koseki from the Analytical Center of our university for mass spectrometry measurements.

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