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Microwave-assisted synthesis of 2-styryl-1,3,4-oxadiazoles from cinnamic acid hydrazide and triethyl orthoesters

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ABSTRACT

A novel and efficient synthesis of 2-styryl-1,3,4-oxadiazoles by cyclocondensation of cinnamic acid hydrazide and triethyl orthoesters under microwave irradiation is reported.

1,3,4-Oxadiazoles belong to an important class of bioactive compounds with a broad spectrum of pharmaceutical and agricultural applications.[1] Conjugated macrocyclic arrangements possessing a 1,3,4-oxadiazole backbone exhibit interesting electron-transfer or luminescent properties and are used in organic light-emitting diodes (OLED), optical brighteners, and laser dyes.[2] One subgroup of the 1,3,4-oxadiazole family of potential interest in display technology is 2-styryl-1,3,4-oxadiazole and its derivatives.[3]

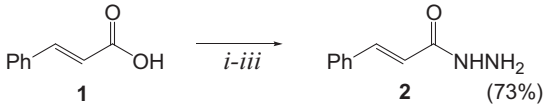
The most common approach toward the preparation of this particular group of compounds involves coupling of acylhydrazides with carboxylic acids in the presence of reagents such as CDI as the activating agent and Ph_3P/CBr_4, cyanuric chloride as the coupling reagent and an indium catalyst, or by the reaction of acylhydrazides with *N*-acylbenzotriazoles.[4] Another convenient method comprises cyclodehydration of 1,2-diacylhydrazines promoted by $POCl_3$.[5]

Recently, we reported on the selective and efficient synthesis of 2-(1-phenyl-1-N-protected-aminomethyl)-1,3,4-oxadiazoles via the reactions of N-protected phenylglycine hydrazides and triethyl orthoesters.[6] In continuation of our interest on the application of acid hydrazides as potent reagents for the synthesis of heterocycles, we studied the preparation of 2-styryl-1,3,4-oxadiazoles utilizing cinnamic acid hydrazide and triethyl orthoesters. To the best of our knowledge, the synthesis of 2-styryl derivatives making use of the above-mentioned reagents has not been reported.

The key compound in the synthesis of 2-styryl-1,3,4-oxadiazoles was cinnamic acid hydrazide (**2**). This molecule was obtained from commercially available cinnamic acid (**1**) according to a short procedure described in the literature.[7] First, acid **1** was converted into its potassium salt and then treated with ethyl chloroformate and finally hydrazine hydrate. The reaction conducted at low temperature resulted in the formation of the desired hydrazide **2** in a 73% yield (Scheme 1). It is worth mentioning that typical synthetic procedures for hydrazides, based on hydrazine hydrate and acid derivatives such as esters or acid chlorides, failed in the case of cinnamic acid hydrazide and gave 3-hydrazino-3-phenylpropionic acid hydrazide, 3-phenyl-5-pyrazolidone,[7] or symmetrically substituted 1,2-bis(3-phenyl-2-propenoyl)hydrazine, respectively.[8]

Our first trials concerning the conventional heating (method A) of the starting hydrazide **2** with excess triethyl orthoester (R = H, Me, Et, Ph, Scheme 2) in glacial acetic acid, resulted in the formation of the desired 2-styryl-1,3,4-oxadiazoles in high yields (80–95%, Table 1). Generally, the reaction yields increased with the increasing bulk of the substituent on the orthoester and the best result was obtained in the case of the reaction conducted with triethyl orthobenzoate (**3d**, 95%, Table 1). A similar trend was observed in previously studied reactions starting from N-protected α-aminocarboxylic acids and orthoesters.[6]

However, long the reaction times (9–40 h, Table 1) and the formation of side products made the conventional method less attractive in comparison to others. We thus decided to carry out



Scheme 1. Synthesis of cinnamic acid hydrazide. Reagents and conditions: (i) KOH, H_2O; (ii) $ClCOOC_2H_5$, CH_2Cl_2, pyridine, 0 °C, 2 h; (iii) $N_2H_4{\cdot}H_2O$, CH_2Cl_2, 0 °C, 12 h.

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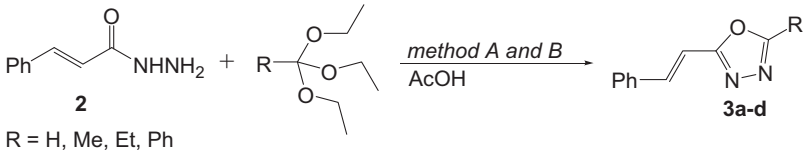

Scheme 2. Reaction of cinnamic acid hydrazide with triethyl orthoesters: method A—conducted using excess orthoester in the presence of AcOH (reflux, 9–40 h); method B—conducted under microwave irradiation at 125 °C, 10 min.

Table 1
Products of the reaction of cinnamic acid hydrazide (**2**) with triethyl orthoesters

Product	R	Method A		Method B		Mp (°C)
		Yield[a] (%)	Time (h)	Yield[a] (%)	Time (min)	
3a	H	80	40	95	10	170–172
3b	Me	82	38	96	10	112–114
3c	Et	86	30	95	10	83–85
3d	Ph	95	9	98	10	128–130[4c]

[a] Yield with respect to the starting hydrazide **2**.

the same reactions under microwave irradiation (method B). A ten-minute irradiation time was sufficient to complete the reaction and produce the title 1,3,4-oxadiazoles **3a–d** exclusively, in excellent yields, as summarized in Table 1. The new products were characterized by elemental analysis and spectroscopic methods.[9]

In conclusion, we have developed an easy and efficient method to synthesize 5-substituted 2-styryl-1,3,4-oxadiazoles from cinnamic acid hydrazide and commercially available triethyl orthoesters.[9] This method has the advantage of providing the desired products rapidly and in high yields which makes it a useful addition to the existing synthetic procedures.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.152.

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9. *Representative procedure—(method B)*: A reaction mixture composed of cinnamic acid hydrazide (**2**) (0.50 g, 3.0 mmol), triethyl orthopropionate (1.2 mL, 1.06 g, 6.0 mmol), and glacial AcOH (2 mL) was placed into a 10 mL thick-walled glass tube and crimp-sealed. The reaction vessel was placed in a CEM Discover microwave-enhanced synthesis system operating at 125 ± 5 °C, power 250 W and irradiated for 10 min. After cooling, the excess orthoester and AcOH were evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel using an eluent of benzene/AcOEt, 1:5, v/v. The pure 5-ethyl-2-styryl-1,3,4-oxadiazole (**3c**) was obtained in a 95% yield as a white solid; mp 83–85 °C; R_f (benzene/AcOEt, 1:5 v/v) 0.55; [Found: C, 71.89; H, 5.98; N, 13.95. $C_{12}H_{12}N_2O$ requires C, 71.97; H, 6.05; N, 13.98%]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (3H, t, *J* 7.5 Hz, CH_2CH_3), 2.89 (2H, q, *J* 7.5 Hz, CH_2CH_3), 7.29 (1H, d, *J* 16.2 Hz, Ph–CH=C*H*–), 7.37–7.45 (3H, m, Ph: H3′, H4′, H5′), 7.53 (1H, d, *J* 16.2 Hz, Ph–*CH*=CH–), 7.73–7.77 (2H, m, Ph: H2′, H6′). ^{13}C NMR (DMSO-d_6): δ 10.4 (CH_2CH_3), 18.4 (CH_2CH_3), 110.2 (Ph–CH=CH–), 127.7, 128.9, 129.8, 134.7 (Ph), 138.1(Ph–*CH*=CH–), 163.8 (C2), 167.0 (C5). IR (ATR) *v*: 3159, 3060, 2940, 2161, 1979, 1648, 1570, 1524, 1479, 1446, 1397, 1380, 1188, 1075, 1032, 1001, 991, 976, 923, 856, 801, 788, 757, 707, 688, 674 cm^{-1}.