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Agnieszka Kudelko, Monika Wróblowska

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An efficient synthesis of conjugated 5-aryl-1,3,4-oxadiazoles from 3-heteroarylacrylohydrazides and acid chlorides

Agnieszka Kudelko*, Monika Wróblowska

Department of Chemical Organic Technology and Petrochemistry, The Silesian University of Technology, Krzywoustego 4, PL-44100 Gliwice, Poland

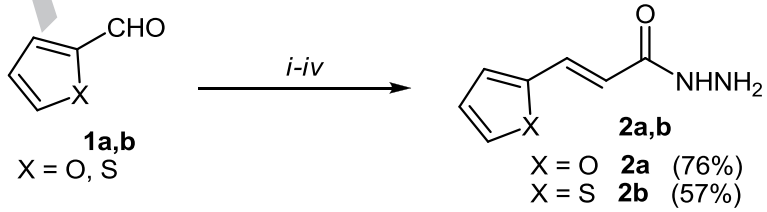
Abstract – New derivatives of 5-aryl-2-[2-(2-furyl)ethenyl]-1,3,4-oxadiazoles and 5-aryl-2-[2-(2-thienyl)ethenyl]-1,3,4-oxadiazoles are synthesized in a stepwise procedure through intermediate acyclic *N′*-arylcarbonyl-*N*-[2-(2-heteroaryl)acryloyl]hydrazines, starting from 3-(2-heteroaryl)acrylic acid hydrazides and acid chlorides. A facile one-pot methodology leading to the final 1,3,4-oxadiazoles is also described.

Keywords: cyclization; heterocycles; 1,3,4-oxadiazoles; 3-heteroarylacryloylhydrazide

Non-naturally occurring five-membered 1,3,4-oxadiazoles have been the subject of significant interest.[1] Many 1,3,4-oxadiazole-containing arrangements exhibit a broad spectrum of biological activity including antibacterial,[2] anti-inflammatory,[3] anticonvulsant,[4] antitumor[5] and antihypertensive.[6] Apart from in medicine, biological interactions of this class are also utilized in agriculture in crop protection (herbicides, fungicides, insecticides).[7] Symmetrically substituted derivatives of 2,5-diphenyl-1,3,4-oxadiazole are also known for their corrosion inhibitory effects.[8] 1,3,4-Oxadiazoles are also studied intensely due to their important electronic properties, which make them potentially useful targets for materials science. Many are used in organic light-emitting diodes (OLEDs), optical brighteners, and laser dyes.[9] Of particular interest are systems based on extended 1,3,4-oxadiazole π-conjugated hybrids, connected directly or indirectly to other electron-deficient systems such as pyridines, furans, thiophenes, phenoxazines and naphthalenes.[10] Such potential luminophores are able to electropolymerize with the formation of linear conducting polymers showing strong electroluminescence.

In continuation of our studies on the application of acid hydrazides in the synthesis of selected heterocyclic arrangements, we have elaborated methodologies for the synthesis of 1,3,4-oxadiazoles conjugated *via* an ethenyl linker to benzene, thiophene and furan rings.[11] These were obtained by cyclocondensation of the appropriate α,β-unsaturated acid hydrazides with triethyl orthoesters, both by conventional heating and under microwave irradiation. However, due to the limited number of commercially available orthoesters (R = Me, Et, Ph), the range of final conjugated products was reduced. Furthermore, compounds substituted with alkyl groups did not show interesting electronic properties and did not undergo electropolymerization. Bearing in mind all these facts, we decided to focus on the synthesis of novel 1,3,4-oxadiazoles containing aryl substituents at position 5, and to investigate another reaction path making use of the same α,β-unsaturated acid hydrazides and aryl chlorides instead of orthoesters. To the best of our knowledge, this stepwise methodology proceeds *via N,N′*-diacylhydrazines and needs the presence of a cyclodehydrating agent such as polyphosphoric acid, boron trifluoride-diethyl etherate, thionyl chloride, phosphorus oxychloride or the Burgess reagent.[12] These fragment hybrids, not described in literature, are promising monomers for optoelectronic applications because they combine different electron-deficient rings featuring excellent electron-transporting properties with high luminous efficiencies.

The key materials for the synthesis of 1,3,4-oxadiazole hybrids are generally two classes of compounds: hydrazides of α,β-unsaturated carboxylic acids (**2**) and aromatic acid chlorides (**3**). The first group of starting materials – acid hydrazides (**2**) – was obtained in a four-step procedure from commercially available aldehydes: 2-furancarboxaldehyde (**1a**) and 2-thiophenecarboxaldehyde (**1b**), according to the methodology described by us earlier.[11b]



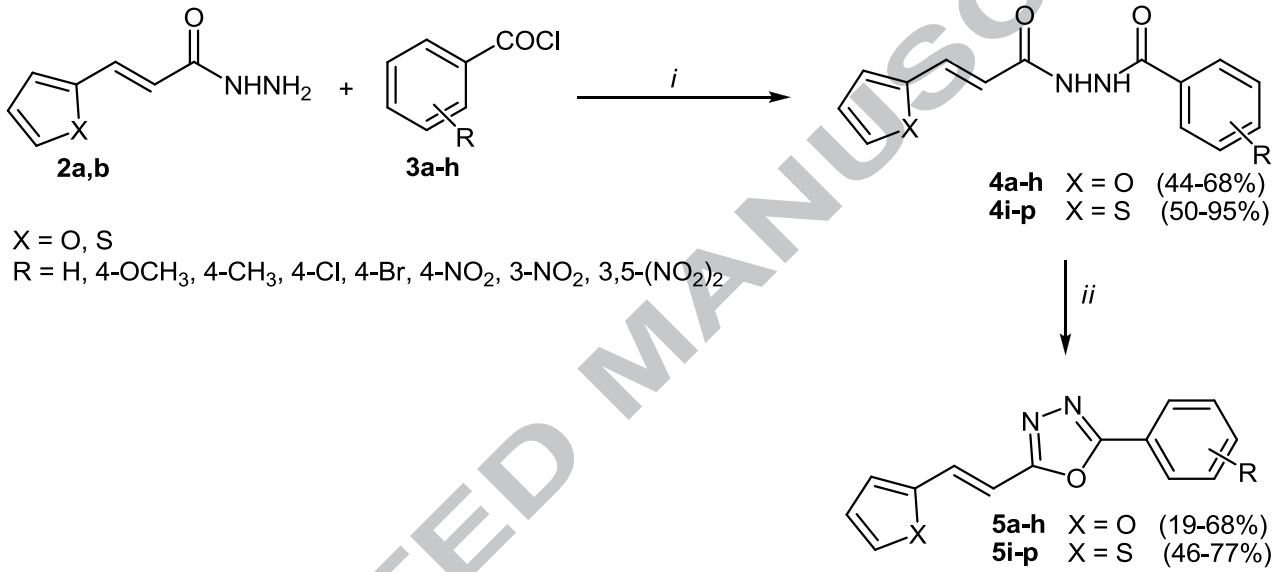
Scheme 1. Synthesis of 3-(2-heteroaryl)acrylic acid hydrazides **2a,b**. Reagents and conditions: (*i*) $CH_2(COOH)_2$, pyridine, piperidine, reflux, 2 h; (*ii*) KOH, H_2O; (*iii*) $ClCOOC_2H_5$, CH_3CN, pyridine, reflux, 2 h; *iv*) $N_2H_4 \cdot H_2O$, CH_3CN, 0 °C, 24 h.

* Corresponding author. Tel.: +48 32 2371729; fax: +48 32 2371021.
E-mail address: Agnieszka.Kudelko@polsl.pl (A. Kudelko).

The initially prepared acids were neutralized with KOH yielding the appropriate salts, which were treated with ethyl chloroformate in acetonitrile. Finally reaction with hydrazine hydrate gave the desired acrylic acid hydrazides in satisfactory yields (**2a,b**, Scheme 1).

Aromatic acid chlorides substituted with electron-donating and electron-withdrawing groups at positions 3 and/or 4 constituted the second group of starting compounds. They were prepared by refluxing the selected carboxylic acids with thionyl chloride in dry toluene until the acids were fully consumed (TLC, 2-8 h).[13] The crude acid chlorides obtained in high yields (**3a-h**, 90-98%) were purified by distillation under reduced pressure and used in the subsequent reactions with acid hydrazides.

The synthesis of the final highly conjugated 1,3,4-oxadiazoles was realized in a two-step sequence *via* *N,N′*-diacylhydrazines (**4**). The reactions were carried out in a two-phase system at low temperature (0-10 °C), in the presence of $NaHCO_3$, playing the role of the binding agent for the evolving HCl gas. Thus, a vigorously agitated basic aqueous solution of 3-(2-heteroaryl)acrylic acid hydrazide **2a,b** was treated with a toluene solution of acid chloride **3a-h**, prepared directly before the main reaction. The acyclic products **4a-p**, resulting from nucleophilic substitution, precipitated immediately after mixing and were purified by recrystallization from the appropriate solvent (AcOH, EtOH). Thus, a range of new derivatives of *N′*-aroyl-*N*-[3-(2-heteroaryl)-2-acryloyl]hydrazines was obtained in moderate yields due to competitive hydrolysis of the aromatic acid chlorides (44-95%, Table 1).[14]



Scheme 2. Synthesis of *N,N'*-diacylhydrazines **4a-p** and 5-aryl-2-[2-(2-heteroaryl)ethenyl]-1,3,4-oxadiazoles **5a-p**. Reagents and conditions: (*i*) $NaHCO_3$, H_2O, toluene, 0-10 °C, 2 h; (*ii*) $POCl_3$, toluene, reflux, 2 h.

Acyclic *N,N′*-diacylhydrazines **4** were heated at reflux with phosphorus oxychloride in dry toluene for a short period of time to give the highly conjugated aromatic derivatives of 5-phenyl-2-[2-(2-furyl)ethenyl]-1,3,4-oxadiazole **5a-h** (19-68%, Table 1) and 5-phenyl-2-[2-(2-thienyl)ethenyl]-1,3,4-oxadiazole **5i-p** (46-77%, Table 1) substituted with electron-donating and -withdrawing groups on the benzene ring. Phosphorus oxychloride, belonging to rather harsh cyclodehydrating agents, is still one of the most often used reagents of this type due to the fact that it is easy accessible, cheap and, what is more important, any side products can be easily removed from the post-reaction mixture. In general, comparing the two series of the final heterocyclic products (X = O, **5a-h** and X = S, **5i-p**), higher yields were observed in the case of compounds containing the more stable thiophene ring (**5i-p**: 46-77%, Table 1). A similar trend was also observed for the acyclic *N,N′*-diacylhydrazines (**4i-p**: 50-95%, Table 1). The identities of the new products (both of *N,N'*-diacylhydrazines and 5-aryl-2-[2-(2-heteroaryl)ethenyl]-1,3,4-oxadiazoles) were confirmed by elemental analyses and spectroscopic methods.

Table 1

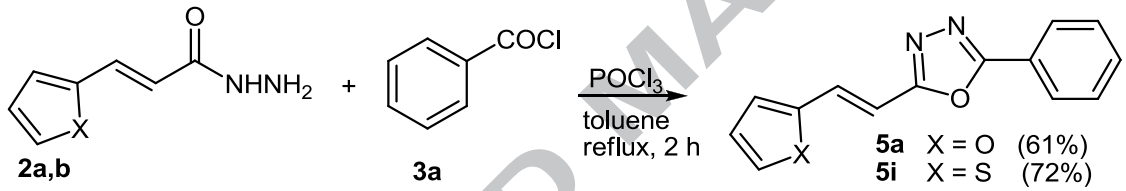
N,N′-Diacylhydrazines **4a-p** and 5-aryl-2-[2-(2-heteroaryl)ethenyl]-1,3,4-oxadiazoles **5a-p** derived from 3-(2-heteroaryl)acrylic acid hydrazides **2a,b** and acid chlorides **3a-h**.

Entry	X	R	*N,N′*-Diacylhydrazine **4**		5-Aryl-2-substituted-1,3,4-oxadiazole **5**	
			Yield[a] (%)	Mp (°C)	Yield[a] (%)	Mp (°C)
a	O	H	64	146-148	19	115-116
b	O	4-OCH_3	44	217-219	45	177-179
c	O	4-CH_3	68	215-217	31	105-107

d	O	4-Cl	56	227-229	44	152-154
e	O	4-Br	48	221-222	34	144-146
f	O	4-NO_2	53	242-244	68	194-195
g	O	3-NO_2	44	254-255	31	202-203
h	O	3,5-$(NO_2)_2$	50	243-245	63	214-215
i	S	H	65	211-213	48	110-113
j	S	4-OCH_3	50	217-218	77	153-155
k	S	4-CH_3	91	216-218	46	121-122
l	S	4-Cl	77	227-229	76	158-161
m	S	4-Br	95	235-237	65	156-157
n	S	4-NO_2	75	267-268	64	210-212
o	S	3-NO_2	58	198-200	69	174-175
p	S	3,5-$(NO_2)_2$	61	> 350	58	237-238

[a] Yield with respect to the starting 3-(2-heteroaryl)acrylic acid hydrazide **2**.

In addition, we decided to investigate the possibility of synthesizing the final 1,3,4-oxadiazoles in a one-pot reaction. Two starting hydrazides: 3-(2-furyl)acrylic acid hydrazide (**2a**) and 3-(2-thienyl)acrylic acid hydrazide (**2b**) and benzoyl chloride (**3a**), which gave the lowest yields in the two-step procedure (overall yields in the stepwise procedure for **5a**: 12%, for **5i**: 31%), were selected to conduct the experiments. Hence, a suspension of the acid hydrazide in dry toluene was treated with a solution of benzoyl chloride in toluene and phosphorus oxychloride ($POCl_3$), and kept at reflux for two hours. After work-up, the heterocyclic products **5a** and **5i** were obtained in considerably higher yields (**5a**: 61%, **5b**: 72%, Scheme 3) compared to the stepwise procedure.[14]



Scheme 3. One-pot synthesis of 5-phenyl-2-[2-(2-furyl)ethenyl]-1,3,4-oxadiazole (**5a**) and 5-phenyl-2-[2-(2-thienyl)ethenyl]-1,3,4-oxadiazole (**5i**).

It is noteworthy that the simplified one-pot synthetic procedure saves reaction time, eliminates the necessity for the separation of intermediates and results in higher yields of the target compounds.

In conclusion, we have reported an efficient approach for the synthesis of highly conjugated 1,3,4-oxadiazoles containing both aryl and heteroarylethenyl units from easy accessible 3-heteroarylacrylohydrazides and acid chlorides, which may find useful applications in optoelectronics. In contrast to the stepwise procedure, the alternative one-pot methodology has the advantage of providing the desired products rapidly and in satisfactory yields.

Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds) associated with this article can be found at….

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14. *Representative procedure – Method A* (*stepwise*): 3-(2-Thienyl)acrylic acid hydrazide (**2b**) (2.55 g, 15 mmol), H_2O (50 mL) and $NaHCO_3$ (1.28 g, 15 mmol) were placed in a two-necked flask, cooled to 0 °C and agitated. Then, benzoyl chloride (2.17 g, 1.8 mL, 15 mmol) in toluene (50 mL) was added dropwise and the mixture agitated at a temperature below 10 °C for 2 h (TLC). The precipitated solid was filtered off, dried under air and recrystallized from EtOH to give *N*′-benzoyl-*N*-[3-(2-thienyl)acrylo]hydrazine (**4i**) (2.65 g, 65%) as a white solid; mp 211-213 °C; R_f ($CHCl_3$/MeOH, 4:1 v/v) 0.68; [Found: C, 61.78; H, 4.39; N, 10.24. $C_{14}H_{12}N_2O_2S$ requires C, 61.75; H, 4.44; N, 10.29%]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.51 (1H, d, *J* 15.6 Hz, α-CH=), 7.13 (1H, dd, *J* 3.2 Hz and *J* 5.2 Hz, C4′-H), 7.45 (1H, d, *J* 3.2 Hz, C3′-H), 7.51 (2H, t, *J* 7.2 Hz, C3′′-H, C5′′-H), 7.58 (1H, d, *J* 7.2 Hz, C4′′-H), 7.65 (1H, d, *J* 5.2 Hz, C5′-H), 7.73 (1H, d, *J* 15.6 Hz, β-CH=), 7.91 (2H, d, *J* 7.2 Hz, C2′′-H, C6′′-H), 10.16 (1H, s, NH), 10.51 (1H, s, NH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 118.0, 127.3, 127.4, 128.4, 128.5, 131.2, 131.8, 132.4, 133.2, 139.5, 164.2, 165.4; UV-VIS (MeOH): λ_{max} 201.5 nm ($\varepsilon \cdot 10^{-3}$ 27.66 $cm^{-1}M^{-1}$), 224.0 (15.06), 310.5 (25.96); IR (ATR) ν: 3231, 2992, 1644, 1623, 1602, 1579, 1507, 1478, 1305, 1273, 1240, 1221, 1137, 1042, 968, 707 cm^{-1}; HRMS: *m/z* calcd for $C_{14}H_{12}N_2O_2S$ $(M+H)^+$: 273.0698. Found 273.0687.

The intermediate **4i** (2.31 g, 8.5 mmol), dry toluene (40 mL) and $POCl_3$ (15 mL, 160 mmol) were heated under reflux for 2 h (TLC). After cooling, the mixture was concentrated on a rotary evaporator, dissolved in dry toluene (30 mL) and washed with H_2O (30 mL). The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The crude 5-phenyl-2-[2-(2-thienyl)ethenyl]-1,3,4-oxadiazole (**5i**) was recrystallized from AcOH/H_2O to yield 1.03 g (48%) of a beige solid; mp 110-113 °C; R_f ($CHCl_3$/MeOH, 4:1 v/v) 0.78; [Found: C, 66.10; H, 3.99; N, 11.01. $C_{14}H_{10}N_2OS$ requires C, 66.12; H, 3.96; N, 11.02%]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (1H, d, *J* 15.6 Hz, α-CH=), 7.03 (1H, dd, *J* 3.6 Hz and 5.2 Hz, C4′-H), 7.22 (1H, d, *J* 3.6 Hz, C3′-H), 7.34 (1H, d, *J* 5.2 Hz, C5′-H), 7.45 (2H, t, *J* 7.6 Hz, C3′′-H, C5′′-H), 7.52 (1H, d, *J* 7.6 Hz, C4′′-H), 7.83 (1H, d, *J* 15.6 Hz, β-CH=), 7.86 (2H, d, *J* 7.6 Hz, C2′′-H, C6′′-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 109.0, 123.9, 126.9, 127.3, 128.1, 128.8, 129.7, 131.5, 132.4, 140.1, 163.9, 164.3; UV-VIS: λ_{max} (MeOH) 202.0 nm ($\varepsilon \cdot 10^{-3}$ 17.57 $cm^{-1}M^{-1}$), 262.5 (11.97), 335.5 (22.62); IR (ATR) ν: 3059, 2163, 1980, 1636, 1550, 1481, 1448, 1013, 958, 775, 716, 687 cm^{-1}; HRMS: *m/z* calcd for $C_{14}H_{10}N_2OS$ $(M+H)^+$: 255.0593. Found 255.0603.

Method B (*one-pot*): 3-(2-Thienyl)acrylic acid hydrazide (**2b**, 2.55 g, 15 mmol) and dry toluene (50 mL) were placed in a two-necked flask equipped with a reflux condenser and dropping funnel and agitated. Benzoyl chloride (2.17 g, 1.8 mL, 15 mmol) in dry toluene (50 mL) was added dropwise to the resulting suspension and the mixture was agitated at room temperature for 10 min and finally $POCl_3$ (25 mL, 267 mmol) was introduced. The mixture was heated under reflux for 2 h (TLC). After cooling, it was concentrated on a rotary evaporator, dissolved in dry toluene (40 mL) and washed with H_2O (40 mL). The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The crude solid **5i** was recrystallized from AcOH/H_2O to yield 2.75 g (72%) of a beige solid; mp 110-113 °C; R_f ($CHCl_3$/MeOH, 4:1 v/v) 0.78.

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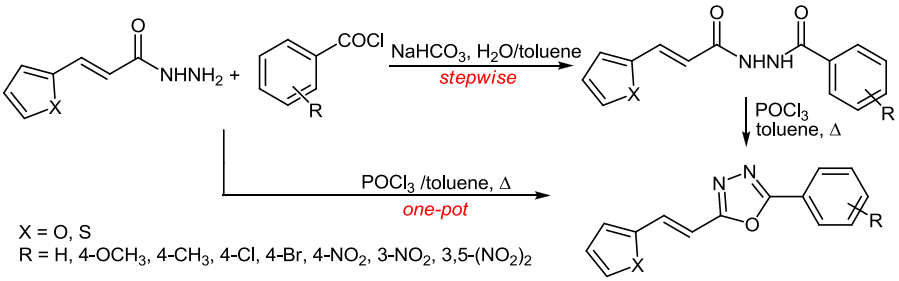

X = O, S

R = H, 4-OCH_3, 4-CH_3, 4-Cl, 4-Br, 4-NO_2, 3-NO_2, 3,5-$(NO_2)_2$