A NEW EFFICIENT ONE-POT SYNTHESIS
OF 2,5-DIARYL-1,3,4-OXADIAZOLES

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Symmetrically substituted 2,5-diaryl-1,3,4-oxadiazoles have been prepared in 81-92% yields by a new direct one-pot synthesis from arenecarboxylic acids, hydrazine dihydrochloride, anhydrous phosphoric acid and sodium borohydride in the absence of a solvent at 170-180°C for 5-6h.
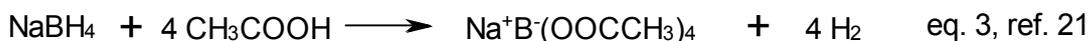
INTRODUCTION

The synthesis of 1,3,4-oxadiazoles is of considerable interest due to their various biological activities, such as analgesic, herbicidal, muscle relaxant, nervous system depressing and tranquilizing properties.[1] At the same time, liquid crystals based on 2,5-diaryl-1,3,4-oxadiazole derivatives have been extensively studied owing to their rich mesophases, good thermal and chemical stability and high photoluminescence quantum yields.[2] Polymers containing 1,3,4-oxadiazoles are known to be useful as electron transporting layers in organic light emitting diodes (LEDs).[3,4]

2,5-Diaryl-1,3,4-oxadiazoles, basic aromatic heterocycles, are usually prepared starting from an aroyl hydrazide and an aroyl chloride. The resulting 1,2-bis(aroyl)-hydrazide intermediate can be cyclized with $POCl_3$,[5] P_2O_5,[6] H_2SO_4,[7] $SOCl_2$,[8] Burgess reagent,[9] triphenylphospine,[10] dimethyldichlorosilane,[11] etc. to form a 2,5-diaryl-1,3,4-oxadiazole. Some other syntheses involve (a) the interaction of trichloromethylarenes with excess of hydrazine hydrate in alcohols which leads to symmetrical 2,5-diaryl-1,3,4-oxadiazoles in 68–98% yields,[12] (b) the condensation of different coumarinoyl hydrazides with various coumarinoyl or quinolinoyl chlorides under microwave irradiation and conventional heating in the presence of sulfamic acid as catalyst,[13] (c) the reaction of aromatic nitriles, hydroxylamine hydrochloride and sodium carbonate in ethylene glycol under heating at 195°C,[14] (d) the interaction of trichloromethylarenes with areneamidoximes in the absence of a solvent at 140-150°C,[15] (e) the reaction between aromatic carboxylic acids and hydrazine hydrate with excess of polyphosphoric acid at high temperatures,[16] (f) the condensation reaction of carboxylic acids with acylhydrazides in the presence of propylphosphonic anhydride.[17]

Sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$) are widely used for the reduction of carbonyl groups. Both reagents are ready sources of hydride ion (H^-), a very strong base and a good nucleophile. Unlike lithium aluminum hydride, which is extremely reactive and reduces the C=O group in aldehydes, ketones, carboxylic acids, esters and amides, sodium borohydride is a much milder reducing agent and it is efficient only with aldehydes and ketones. The reduced reactivity of $NaBH_4$ allows it to be used even in alcohol or aqueous solvents, whereas $LiAlH_4$ reacts violently with these solvents to produce hydrogen gas. Although $NaBH_4$ does not reduce carboxylic acids, it may react slowly or vigorously with acids when hydrogen gas is liberated and salts of the acid are formed. For example, when using acetic acid different reactive intermediates result and the following reactions take place:

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$$NaBH_4 \; + \; CH_3COOH \longrightarrow Na^+B^-H_3OOCCH_3 \; + \; H_2 \qquad \text{eq. 1, ref. 18}$$

$$NaBH_4 \; + \; 3\,CH_3COOH \longrightarrow Na^+B^-H(OOCCH_3)_3 \; + \; 3\,H_2 \qquad \text{eq. 2, ref. 19, 20}$$

$$NaBH_4 \; + \; 4\,CH_3COOH \longrightarrow Na^+B^-(OOCCH_3)_4 \; + \; 4\,H_2 \qquad \text{eq. 3, ref. 21}$$

In a previous work, we found that sodium tetraacetoxyborate obtained according to equation 3 and prepared *in situ* in acetic acid solution, reacts with aromatic aldehydes to give the corresponding cinnamic acids.[22]

Concerning the other key-reagent involved in the novel synthesis that we introduce herein, namely phosphoric acid, its use in preparative organic chemistry is less known. Phosphoric acid is not a particularly strong acid, as indicated by its first dissociation constant ($Ka_1=7.5\times10^{-3}$), but it is stronger than acetic acid ($Ka=1.75\times10^{-5}$). One can suppose that H_3PO_4 would react with $NaBH_4$ in a similar fashion to CH_3COOH.

Hydrazine dihydrochloride is used as source of hydrazine, a bifunctional reagent with large applications in organic chemistry, such as synthesis of hydrazones or heterocyclic compounds.

The present work was devoted to the development of a new method for the one-pot synthesis of symmetrical 2,5-diaryl-1,3,4-oxadiazoles from arenecarboxylic acids, hydrazine dihydrochloride, sodium borohydride and excess of anhydrous phosphoric acid, as reagent and solvent as well.

RESULTS AND DISCUSSION

This investigation represents a new route for the direct conversion of carboxylic acids to symmetrical 1,3,4-oxadiazoles in the presence of hydrazine and H_3PO_4, which acts as coupling and cyclodehydration

reagent. The prerequisite of this research work is based on our experimental results, as well as on the complex chemistry of boron. The key step in this reaction system involves a species reactive with the aromatic acid and it is generated *in situ* through the reaction between $NaBH_4$ and H_3PO_4.

Similar to eq. 3, we suppose that $NaBH_4$ can convert the unreactive H_3PO_4 into a complex intermediate, which preserves boron-centered reactive sites and it is able to interact with aromatic carboxylic acids (**I**). The resulting sodium triphosphorylhydroxyborate reacts with hydrazine dihydrochloride (**II**) and the heterocycles (**III**) are subsequently formed by intramolecular cyclodehydration in accordance with Scheme 1. The reaction requires relatively high temperatures (170-180°C) for its completion and needs no solvent because H_3PO_4 used in excess is a good solvent for reagents and resulting products, as well, and it is stable under reaction conditions. As can be seen in Table 1, oxadiazoles (**III**) were obtained in yields ranging from 81 to 92% depending on the structure of their corresponding carboxylic acids. As expected, oxadiazole **IIIf** is prepared in the highest yield because the *p*-CH$_3$ substituent in the structure of benzoic acid induces the highest reactivity. The reaction conditions have also influence on the yield of this reaction. At lower temperatures, the yields decreased. For example, the yield in the product **IIIe** decreased to 40-43% when the reaction was performed at 130-140°C.
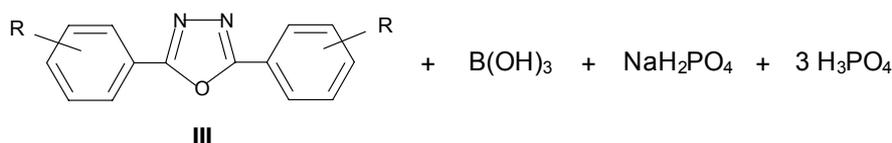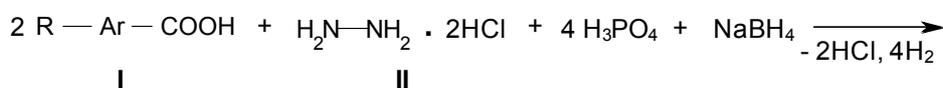
oxadiazole	IIIa	IIIb	IIIc	IIId	IIIe	IIIf
R	H	*o*-Cl	*m*-Cl	*p*-Cl	*m*-CH$_3$	*p*-CH$_3$

Scheme 1– Synthesis of 2,5-diaryl-1,3,4-oxadiazoles from aromatic carboxylic acids, hydrazine dihydrochloride, phosphoric acid and sodium borohydride.

Table 1

Oxadiazoles obtained with phosphoric acid and sodium borohydride

Oxadiazole	**IIIa**	**IIIb**	**IIIc**	**IIId**	**IIIe**	**IIIf**
Yield (%)	81	87	80	84	89	92
Reaction time (h)	5	6	6	6	5-6	5-6
m.p.[b] (°C)	139-141	94-96	161-162	243-245	81-83	174-176

[a] Yield calculated based on the amount of carboxylic acid employed in the reaction;
[b] After recrystallization from ethanol (**IIIa**) and DMF (**IIIb-f**).

Based on literature data[16,23] and our experimental results, the reaction mechanism is illustrated in Scheme 2.

We assume that H_3PO_4 reacts with $NaBH_4$ at 100-120°C in a molar ratio of 4:1 resulting in an intermediate (**A**), the sodium tetraphosphorylborate, and hydrogen as by-product. The role of the reactive complex (**A**) is to activate the aromatic carboxylic acid. The phosphoryl arenecarboxylate (**C**) formed as the result of the above reaction interacts with hydrazine dihydrochloride and 1,2-

bis(aroyl)hydrazide (**D**) is generated. The last step involves the condensative heterocyclization of the resulted *N*-phosphorylhydrazonoate (**E**) and its conversion into 2,5-diaryl-1,3,4-ozadiazole (**III**). The mechanism we have introduced in Scheme 2, and which underpins the reaction between aromatic carboxylic acids and hydrazine illustrated in Scheme 1, is supported by the fact that this reaction does not produce 2,5-diaryl-1,3,4-ozadiazole in the absence of either H_3PO_4 or $NaBH_4$ under the same reaction conditions (5-6 h duration, 170-180°C).
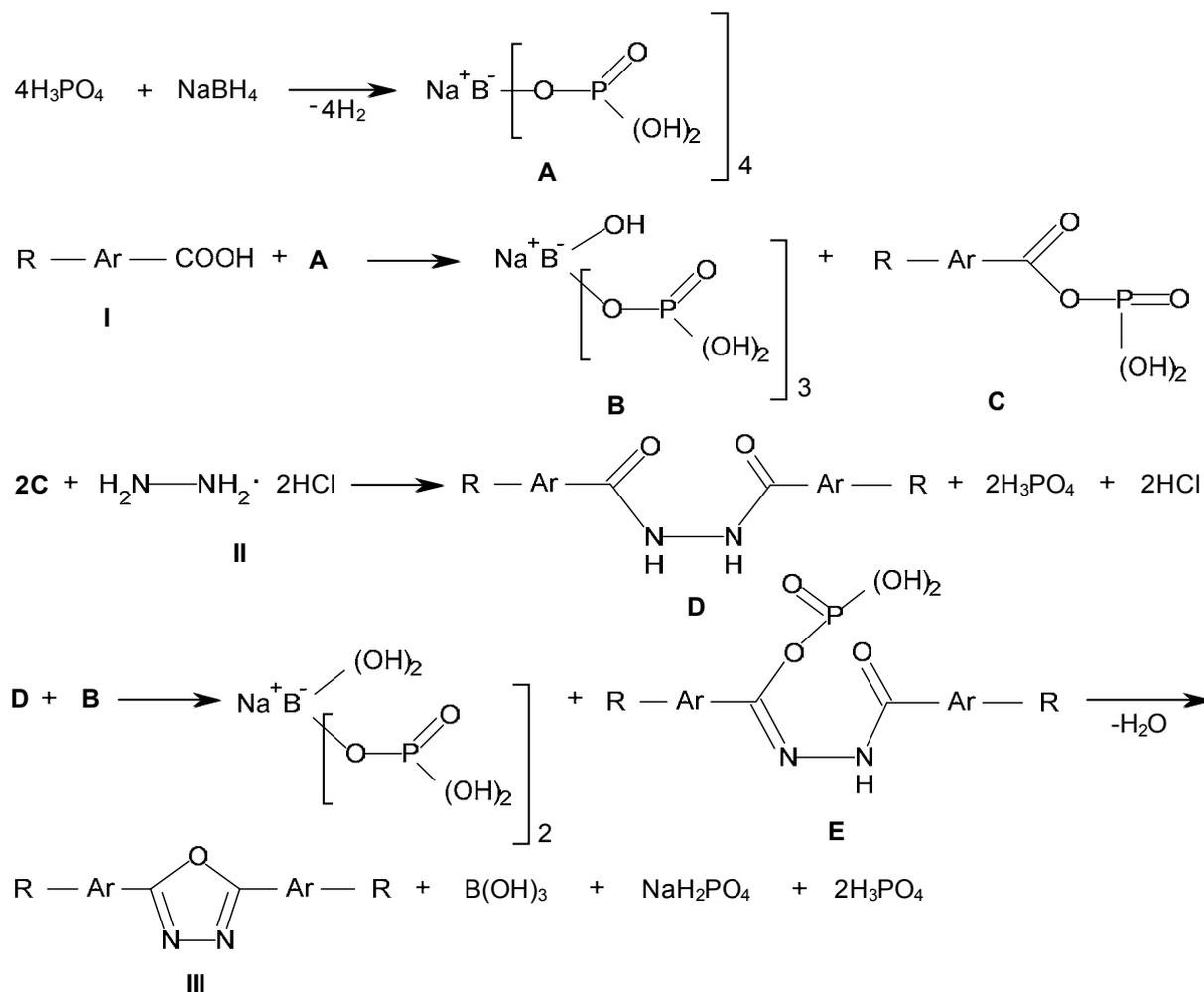
Scheme 2– The proposed mechanism for the reaction of aromatic carboxylic acids with hydrazine dihydrochloride.

Table 2

Elemental analysis and spectral data of 2,5-diaryl-1,3,4-oxadiazoles (**III**)

Oxadiazole	FTIR (ν, cm^{-1}) C=N	^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm)	Molecular formula	Analyses (%) Calc./Found		
				C	H	N
IIIa	1610	8.12 (dd, 4H, *o*-H), 7.51 (m, 6H, *m, p*-H)	$C_{14}H_{10}N_2O$ (222.245)	75.66 75.70	4.57 4.60	12.60 12.54
IIIb	1615	7.86 (d, 2H, *o*-H), 7.56-7.34 (m, 6H, *m, p*-H)	$C_{14}H_8Cl_2N_2O$ (291.136)	57.76 57.81	2.77 2.80	9.62 9.66
IIIc	1612	8.02-7.86 (m, 4H, *o*-H), 7.48-7.39 (m, 4H, *m,p*-H)	$C_{14}H_8Cl_2N_2O$ (292.136)	57.76 57.71	2.77 2.71	9.62 9.57
IIId	1614	7.86 (d, 4H, *o*-H), 7.63 (m, 4H, *m*-H)	$C_{14}H_8Cl_2N_2O$ (291.136)	57.76 57.82	2.77 2.73	9.62 9.67
IIIe	1613	8.05 (br, 2H, *o*-H), 7.47-7.35 (m, 4H, *o,m*-H), 7.01 (d, 2H, *p*-H), 2.32 (s, 3H, CH$_3$)	$C_{16}H_{14}N_2O$ (250.299)	76.78 76.72	5.64 5.69	11.19 11.24
IIIf	1617	8.02 (m, 4H, *m*-H), 7.24 (m, 4H, *o*-H), 2.31 (s, 3H, CH$_3$)	$C_{16}H_{14}N_2O$ (250.299)	76.78 76.83	5.64 5.69	11.19 11.13

The structures of different 2,5-diaryl-1,2,4-oxadiazoles obtained were confirmed by ^{1}H NMR and FTIR spectroscopy (Table 2). The ^{1}H NMR spectra of these products presented signals assigned to aromatic protons and CH$_3$ (**IIIe and IIIf**) and lacked the hydrazide, hydrazono and OH proton signals characteristic to the intermediate compounds. The FTIR spectra showed absorption bands ascribed to C=N bond and no band attributed to P–OH groups (sharp bands around 3665 cm^{-1} and broad bands near 2900 cm^{-1}), CO–NH (sharp bands between 1630-1680 cm^{-1}), NH–NH (3200-3400 cm^{-1}) and P=O (around 1200 cm^{-1}) were evidenced.

EXPERIMENTAL

General procedure for one-pot synthesis of 1,3,4-oxadiazoles: In a 100mL three-neck round-bottom flask, fitted with a mechanical stirrer, a nitrogen inlet and a thermometer, a mixture of 9.8g (0.1 mol) anhydrous phosphoric acid and 0.38g (0.01 mol) sodium borohydride was heated at 100-120°C under stirring for 2-3h in an inert atmosphere. Then, 2.44g (0.02 mol) benzoic acid, 1.05g (0.01 mol) H$_2$N–NH$_2$·2HCl and 1mL xylene were added and the resulted mixture was heated to 170-180°C, under stirring for 5-6h. Xylene was added in order to prevent foaming and sublimation. At the end, the mixture was treated with 15-20 mL HCl 10%. The precipitated was filtered and washed with 10-15mL of water, and dried in a vacuum dessicator.

All starting materials were procured from commercial sources as reagent grade or of high purity and used as received, without further purification.

Spectral measurements of ^{1}H NMR were performed using a Bruker Avance DRX spectrometer at 400 MHz in DMSO-d_6 as solvent. The chemical shifts were expressed in δ values compared to Me$_4$Si, which was used as internal standard.

Infrared spectra were recorded on a Bruker Vertex 70 Fourier transform infrared spectrometer using the KBr pellet technique. Melting points of the resulted 2,5-diaryl-1,3,4-oxadiazoles were measured on a Melt-Temp II (Laboratory Devices) apparatus without correction.

CONCLUSION

A key feature of this reaction was its inherent simplicity in producing 2,5-diaryl-1,3,4-oxadiazoles directly from aromatic carboxylic acids in excellent yields. As H$_3$PO$_4$ and NaBH$_4$ produce only water-soluble by-products, chromatographic isolation of the products was not necessary because the purity of the resulted 2,5-diaryl-1,3,4-oxadiazoles was quite high. NaBH$_4$ is a gentle (and therefore safer) reagent; in addition, NaBH$_4$ and H$_3$PO$_4$ are relatively environmentally friendly because of their low toxicity. Consequently, this one-pot synthesis offers an alternative to classic methods, represents a useful way to prepare such five-membered heterocycles, and highlights the synthetic utility of the two compounds as versatile reagents in organic chemistry.

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