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ORIGINAL PAPER

Electrochemically initiated oxidative cyclization: a versatile route for the synthesis of 5-substituted 2-amino-1,3,4-oxadiazoles

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Abstract A rapid, improved, and environmentally benign synthesis of 5-substituted 2-amino-1,3,4-oxadiazoles by one-pot electrocyclization of acylthiosemicarbazones is reported. Controlled potential electrolysis was performed at room temperature in acetonitrile as non-aqueous solvent and $LiClO_4$ as supporting electrolyte. The reaction products were characterized by spectroscopic methods and a mechanism was deduced from voltammetric data. Better yields at room temperature, shortest reaction time, and easy work-up are attractive features of this green procedure.

Keywords Controlled potential electrolysis · Cyclic voltammetry · Electrochemical synthesis · Electron transfer · Oxadiazoles

Introduction

1,3,4-Oxadiazoles are a class of heterocycles which have attracted significant interest in medicinal chemistry. These compounds have a wide range of pharmaceutical and biological activity including anti-inflammatory [1], antimicrobial [2], antimalarial [3], antifungal [4], muscle relaxant [5], anticancer [6], analgesic [7], anti-HIV [8], antitubercular [9], anticonvulsant [10], antiproliferative [11], insecticidal [12], antiparasitic [13], antiviral [14], antihypoglycemic [15], hypotensive [16], 5-HT-receptor antagonist [17], and muscarinic receptor agonist [18]. Some material applications of 1,3,4-oxadiazole derivatives are in photosensitizers [19], liquid crystals [20], and organic light-emitting diodes (OLEDs) [21].

Development of eco-friendly synthetic methods in chemical research has great importance [8, 22–28] because conventional organic synthesis involves multistep procedures with complex isolation, and expensive and toxic solvents and reagents. With increasing public concern over environmental degradation, use of electrochemical technology can be a valuable alternative to conventional reagents for fine chemical synthesis [29–31]. Because of electron transfer between an electrode and substrate molecules, formation of highly reactive intermediates is achieved under mild conditions, avoiding acids and bases as reducing or oxidizing agents and related waste by-products. It seems that electrochemical procedures will emerge as a new tool in which the special advantages of electrochemistry, for example energy specificity, chemical selectivity, and specific activation of small molecules can be applied without toxic reagents and solvents.

Results and discussion

1,3,4-Oxadiazoles are an important class of heterocyclic compounds with a wide range of pharmaceutical and biological activity. Their synthesis and transformation have been of interest for a long time, as documented by a steadily increasing number of publications and patents [32]. However, despite their common use, various reported methods for preparation of 1,3,4-oxadiazoles [9] suffer from harsh conditions or stoichiometric formation of

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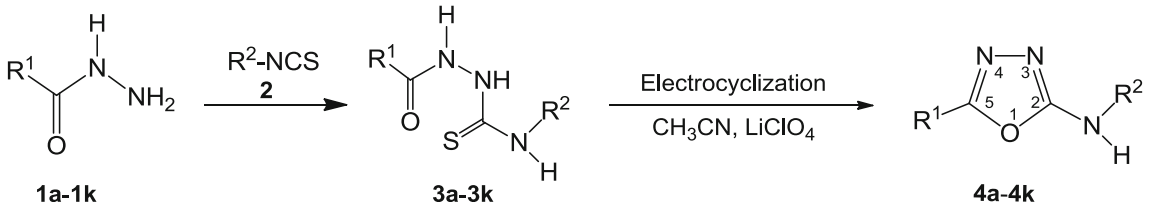
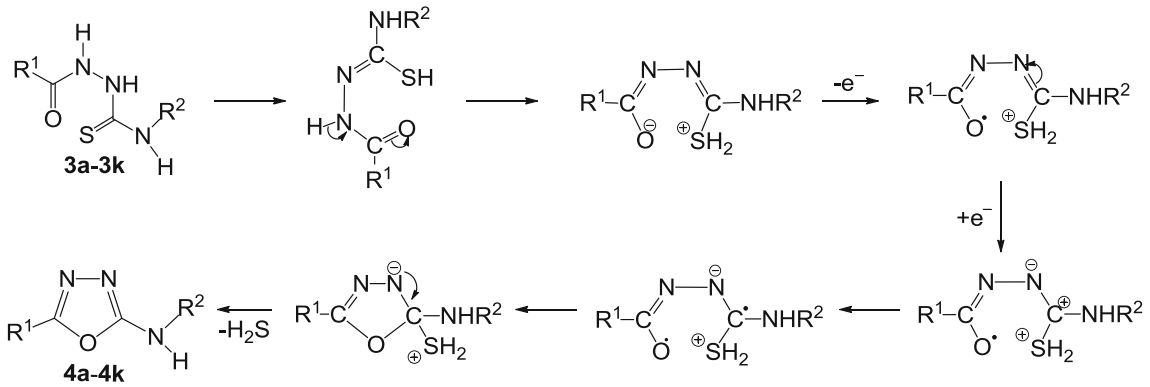


Scheme 1



Scheme 2

byproducts. Approaches are based on bromine oxidation of semicarbazide derivatives and on cyclodesulfurization of acylthiosemicarbazide derivatives in solution using I_2/NaOH or 1,3-dicyclohexylcarbodiimide (DCC) [33–36], mercury(II) acetate or yellow mercury(II) oxide [37, 38], and highly reactive alkylating agents, for example methyl iodide [39] and ethyl bromoacetate [9]. Evans [40] synthesized oxadiazole derivatives by parallel synthesis in an efficient one-pot preparation using resin-bound reagents. All these methods are usually carried performed in different synthetic steps and require high temperature, and extraction and purification of the products from the mixture requires great precautions.

The objective of our research program is to find a new general route for eco-friendly efficient synthesis [41–46] of important organic compounds without the use of toxic reagents. We propose electrooxidative cyclization of acylthiosemicarbazones **3** in the presence of acetonitrile as solvent and $LiClO_4$ as background electrolyte. The reaction involves two discrete synthetic steps; in the first step, reaction of acylhydrazide **1** with an isothiocyanate **2** provides the acylthiosemicarbazone **3**. In the second step, electrooxidative cyclization of acylthiosemicarbazone **3** gives oxadiazoles **4** (Scheme 1).

In the proposed mechanism (Scheme 2) the acylthiosemicarbazone undergoes one-electron oxidation followed by dehydrosulfidation, i.e., evolution of H_2S (confirmed by use of lead tetraacetate paper) and results in the formation of products in 70–95% yield.

Experimental

Cyclic voltammetric experiments were performed using an Alsch Instruments model 600A electrochemical analyzer. IR spectra (KBr) were recorded on a Shimadzu 8201 PC IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer (400 MHz) in $CDCl_3$ using TMS as an internal standard. Chemical shifts (δ) are quoted in ppm. Mass spectra were acquired on a Jeol SX-1020/PA-6000 (EI) spectrometer. Melting points were determined by the open tube capillary method.

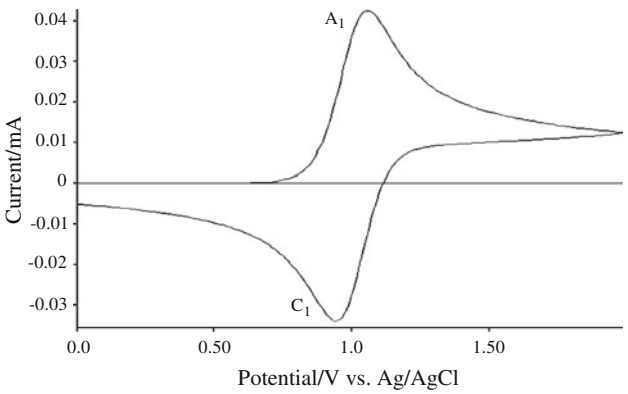


Fig. 1 Cyclic voltammogram of **3a** in 0.1 M $LiClO_4$ at a platinum electrode (area 1 × 1 cm^2) at a scan rate of 100 mV s^{-1}, counter electrode: platinum mesh, reference electrode: Ag/AgCl, $T = 25 \pm 1$ °C. The corresponding CV contains one anodic peak at 1.24 V. This peak corresponds to oxidation of acylthiosemicarbazone

Table 1 Current–potential data, yields, and melting points of 5-substituted 2-amino-1,3,4-oxadiazoles **4a–4k** from electroorganic synthesis

Product	R^1	R^2	Time/h	Applied potential/V	Current/A	Yield/%	M.p. (Lit. m.p.)/°C
4a	4-C_5H_4N	C_6H_5	3	1.24	0.04	90	267 (266–268 [47])
4b	4-C_5H_4N	*o*-$CH_3C_6H_4$	3	1.33	0.07	92	276 (276–278 [47])
4c	4-C_5H_4N	*p*-$CH_3C_6H_4$	3	1.52	0.04	90	279 (278–280 [47])
4d	4-C_5H_4N	*o*-$OCH_3C_6H_4$	4	1.40	0.06	95	237 (236–238 [47])
4e	4-C_5H_4N	*p*-$OCH_3C_6H_4$	4	1.42	0.05	88	281 (280–282 [47])
4f	4-C_5H_4N	*p*-Cl-C_6H_4	3	1.44	0.04	85	238 (238–240 [47])
4g	β-$C_{10}H_7$-O-CH_2	CH_3	3	1.46	0.06	70	139 (139–141 [48])
4h	β-$C_{10}H_7$-O-CH_2	C_2H_5	3	1.28	0.07	72	140 (140–141 [48])
4i	β-$C_{10}H_7$-O-CH_2	CH_2-CH=CH_2	4	1.30	0.09	87	134 (134–135 [48])
4j	β-$C_{10}H_7$-O-CH_2	C_6H_5	3	1.33	0.08	85	142 (141–142 [48])
4k	β-$C_{10}H_7$-O-CH_2	*m*-Cl-C_6H_4	3	1.42	0.05	75	202 (203 [49])

All chemicals used were AnalaR grade purchased from Merck and Loba Chem, and were used without purification. Water used in the reaction was double-distilled. The acylthiosemicarbazones **3** were prepared by acylation of commercially available hydrazides **1** with the appropriate isothiocyanates **2** by a known method [28] (Fig. 1).

*Electroorganic synthesis of 5-substituted 2-amino-1,3,4-oxadiazoles **4a–4k** — controlled potential electrolysis (CPE)*

Acylthiosemicarbazone **3** (8.0 mmol) and lithium perchlorate (4.0 mmol) were dissolved in 100 cm^3 acetonitrile. Preparative-scale controlled potential electrolysis was performed at room temperature in a 250 cm^3 three-electrode cell with platinum plate (flattened sheet of dimensions 1.0 cm × 1.0 cm) as working and counter electrodes and saturated calomel electrode (SCE) as reference electrode. A magnetic stirrer was used to ensure complete mixing of the reaction mixture during electrolysis. All electrolysis reactions were carried out at the corresponding oxidation potential of the substrate (1.24 V for **3a**) and were complete in 3–4 h. The progress of the reactions was monitored by TLC. The current–potential data were recorded by use of a potentiostat at intervals of 15 min and are listed in Table 1. After electrolysis the solvent was evaporated under reduced pressure and the product was purified by column chromatography over silica gel. All products were analyzed by spectral techniques.

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