# SYNTHESIS OF 5-ARYL-1,3,4-OXADIAZOLYL-2-ACETIC ACIDS

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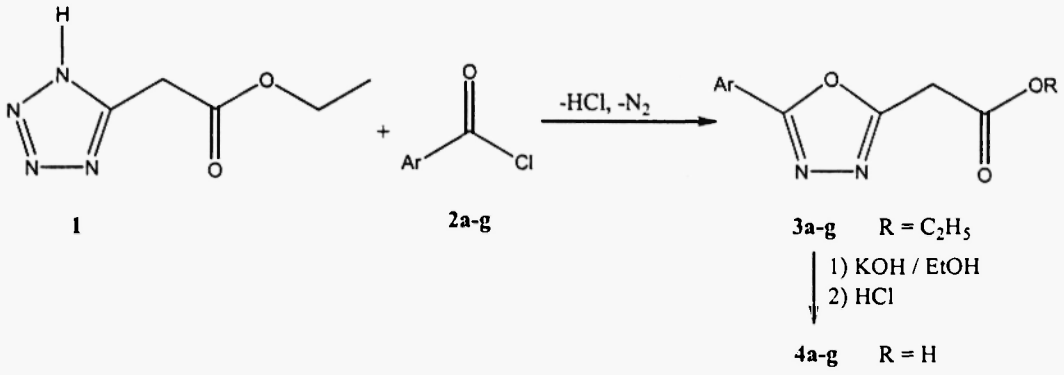
**Abstract:** Ethyl (1*H*-tetrazol-5-yl)acetate is acylated with aroyl chlorides and heteroaroyl chlorides in pyridine. The intermediate acyltetrazoles undergo thermal degradation to ethyl (5-aryl-1,3,4-oxadiazol-2-yl)acetates and (5-heteroaryl-1,3,4-oxadiazol-2-yl)acetates, respectively, in good yields. The corresponding acetic acids are obtained by potassium hydroxide mediated hydrolysis of the esters in anhydrous ethanol.

## Introduction

Heteroaryl acetic acids often posses anti-inflammatory and analgesic activities [1,2] and are used in the synthesis of new beta-lactam antibiotics with anti-microbial activity.[3,4] Aryloxadiazolyl acetic acids and their derivatives are no exception and their biological activities are well known. [5,6] The previously described multistep syntheses of aryloxadiazolylacetic acids are based on the cyclization of 1,2-diacylhydrazines [6-8] or substituted benzoylhydrazines [9-11] and are inefficient.

A simple synthesis of ethyl aryloxadiazolylacetates **3** is described in this paper. The method is based on acylation of ethyl (1*H*-tetrazol-5-yl)acetate (**1**) with aroyl chlorides **2** followed by thermal degradation of the acylated tetrazoles to 1,3,4-oxadiazoles **3**. Hydrolysis of **3** furnishes acids **4**.

Acylation of 5-aryl-1*H*-tetrazoles and a subsequent thermal degradation leading to 2,5-diaryl-[1,3,4]oxadiazoles is known. [12-14] This approach has been used in the preparation of several diaryl oxazoles [15] and arylalkyl oxazoles. [16] However, it has never been used for the preparation of oxadiazolylacetic acids starting from esters of (1*H*-tetrazol-5-yl)-acetic acid. This apparently overlooked application of the general method enhances its synthetic utility and provides a simple two-step synthetic route to aryloxadiazolylacetic acids **4**.




a: Ar = phenyl, b: 4-methylphenyl, c: 4-methoxyphenyl, d: 2-chlorophenyl, e: 2-methoxyphenyl, f: 2-furanyl, g: 2-thienyl

## Results and Discussion

The simplicity of this preparative method is demonstrated on a 30g scale of starting ethyl 1*H*-tetrazole-5-acetate (**1**) and its versatility is shown by using several aroyl chlorides and heteroaroyl chlorides **2** in the syntheses. A simple addition of an aroyl chloride to a cold pyridine solution of **1** followed by heating of the mixture at 50 °C accomplished the acylation of the starting tetrazole **1**. The thermal decomposition of the intermediate acyltetrazole started around 60 °C as evidenced by the evolution of nitrogen and was completed after 45 min under reflux conditions. The decomposition was gradual and no sudden exothermic reaction was observed on this reaction scale. Crude ethyl esters **3** were obtained as red oils in 70-90% yields and some of them solidified on standing for several days. In most cases the crude esters could be used for hydrolysis without further purification. However, simple flash chromatography on silica gel (cyclohexane/triethylamine/ethanol , 15:2:1) gave pure esters **3** in 35-76% yields. Subsequent crystallization from *tert*-butyl methyl ether/cyclohexane or ethyl acetate/cyclohexane gave pure analytical samples of **3**.

It is known that 1,3,4-oxadiazoles are sensitive to heating in strongly basic aqueous solutions.[7] Thus, hydrolysis of the ester **3b** in aqueous ethanol resulted in partial decomposition of the 1,3,4-oxadiazole ring to give 2-(4-methylbenzoyl)hydrazide of malonic acid as a by-product that contaminated the desired acid **3b**. In order to avoid the oxadiazole ring cleavage the hydrolysis of esters **3** with potassium hydroxide was conducted in anhydrous ethanol.[7] Final purification of 4 was accomplished by crystallization from 80% aqueous ethanol.

Biological activity of acids **4** as anti-inflammatory and analgesic agents will be reported in due course. Work is in progress to utilize these acids in the synthesis of new beta-lactam antibiotics.

## Experimental

All reagents were obtained from Aldrich. Melting points (Pyrex capillary) are uncorrected. The $^1$H NMR spectra of esters **3** and acids **4** were run at 60 MHz in deuteriochloroform and deuterated dimethyl sulfoxide, respectively, with tetramethylsilane as an internal reference. All compounds gave satisfactory results of elemental analysis.

**General Procedure for Preparation of Esters 3a-3g.** An aroyl chloride (0.21 mol) was added at 10 °C to a stirred solution of ethyl (1*H*-tetrazol-5-yl)acetate [17,18] (30g, 0.19 mol) in pyridine (200 mL). A cold bath was removed and the solution was heated at 50 °C for 1 h followed by reflux for 45 min until evolution of nitrogen ceased. After cooling the mixture was poured into water (1L) and acidified with hydrochloric acid (215 mL, 2.62 mol). Crude oily ester was extracted with ethyl acetate (500 mL), and the extract was washed with aqueous potassium carbonate solution, water, dried over magnesium sulfate, and concentrated. The crude ester was purified further by flash chromatography (cyclohexane/triethylamine/ethanol, 15:2:1). Yields for the esters are given after flash chromatography.

Ethyl (5-phenyl-[1,3,4]oxadiazol-2-yl)acetate (**3a**): yield 44%; mp 70-72 °C (from *tert*-butyl methyl ether/cyclohexane); $^1$H NMR δ 1.28 (t, J = 7 Hz, 3H), 4.05 (s, 2H), 4.26 (q, J = 7 Hz, 2H), 7.46-7.58 (m, 3H), 8.07 (m, 2H).

Ethyl (5-(4-methylphenyl)-[1,3,4]oxadiazol-2-yl)acetate (**3b**): yield 51%; mp 46-48 °C (from ethyl acetate/cyclohexane); $^1$H NMR δ 1.30 (t, J = 7 Hz, 3H), 2.43 (s, 3H), 4.05 (s, 2H), 4.25 (q, J = 7 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 7.95 (d, J = 8 Hz, 2H).

Ethyl (5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl)acetate (**3c**): yield 76%; mp 67-69 °C (from ethyl acetate/cyclohexane); $^1$H NMR δ 1.30 (t, J = 7 Hz, 3H), 3.90 (s, 3H), 4.00 (s, 2H), 4.25 (q, J = 7 Hz, 2H), 7.00 (d, J = 9 Hz, 2H), 8.00 (d, J = 9 Hz, 2H).

Ethyl (5-(2-chlorophenyl)-[1,3,4]oxadiazol-2-yl)acetate (**3d**): yield 75%; oil; bp 185 °C/1 mmHg; $^1$H NMR δ 1.28 (t, J = 7 Hz, 3H), 4.07 (s, 2H), 4.27 (q, J = 7 Hz, 2H), 7.38-7.59 (m, 3H), 7.96 (d, J = 7 Hz, 1H).

Ethyl (5-(2-methoxyphenyl)-[1,3,4]oxadiazol-2-yl)acetate (**3e**): yield 40%; oil; $^1$H NMR δ 1.27 (t, J = 7 Hz, 3H), 3.95 (s, 3H), 4.05 (s, 2H), 4.24 (q, J = 7 Hz, 2H), 7.07 (m, 2H), 7.50 (m, 1H), 7.92 (m, 1H).

Ethyl (5-(2-furanyl)-[1,3,4]oxadiazol-2-yl)acetate (**3f**): yield 35%; oil; $^1$H NMR δ 1.28 (t, J = 7 Hz, 3H), 4.04 (s, 2H), 4.24 (q, J = 7 Hz, 2H), 6.60 (m, 1H), 7.18 (m, 1H), 7.64 (m, 1H).

Ethyl (5-(2-thienyl)-[1,3,4]oxadiazol-2-yl)acetate (**3g**): yield 55%; mp 38-39 °C (from ethyl acetate/cyclohexane); $^1$H NMR δ 1.30 (t, J = 7 Hz, 3H), 4.03 (s, 2H), 4.23 (q, J = 7 Hz, 2H), 7.18 (m, 1H), 7.57 (m, 1H), 7.77 (m, 1H).

**General procedure for Preparation of Acids 4a-4g**. A solution of potassium hydroxide (6.2g, 0.11 mol) in ethanol (620 mL) was added to a solution of ethyl ester **3** (0.1 mol) in ethanol (500 mL), and the mixture was stirred at room temperature for 3 h. Precipitated potassium salt of the acid was suction filtered, dissolved in water (250 mL) and acidified with hydrochloric acid (13 mL, 0.13 mol). In the cases when the potassium salt did not precipitate from ethyl alcohol solution, the solution was concentrated, and the residue was dissolved in water (250mL) and extracted with ethyl acetate (100 mL). Acidification of the aqueous layer with hydrochloric acid (13 mL, 0.13 mol) caused precipitation of acid **4**. The crude acid was crystallized from aqueous ethanol.

(5-Phenyl-[1,3,4]oxadiazol-2-yl)acetic acid (**4a**): yield 80%; mp 113-114 °C; $^1$H NMR δ 4.16 (s, 2H), 7.57-8.00 (m, 5H), 13.20 (s, 1H).

(5-(4-Methylphenyl)-[1,3,4]oxadiazol-2-yl)acetic acid (**4b**): yield 83%; mp 121-122 °C;
$^1$H NMR δ 2.40 (s, 3H), 4.16 (s, 2H), 7.40 (d, J = 7 Hz, 2H), 7.85 (d, J = 7 Hz, 2H), 13.20 (s, 1H).

(5-(4-Methoxyphenyl)-[1,3,4]oxadiazol-2-yl)acetic acid (**4c**): yield 85%; mp 123-124 °C;
$^1$H NMR δ 3.83 (s, 3H), 4.17 (s, 2H), 7.16 (d, J = 7 Hz, 2H), 7.94 (d, J = 7 Hz, 2H), 13.17 (s, 1H).

(5-(2-Chlorophenyl)-[1,3,4]oxadiazol-2-yl)acetic acid (**4d**): yield 74%; mp 117-119 °C;
$^1$H NMR δ 4.18 (s, 2H), 7.50-7.96 (m, 4H), 13.20 (s, 1H).

(5-(2-Methoxyphenyl)-[1,3,4]oxadiazol-2-yl)acetic acid (**4e**): yield 72%; mp 88-89 °C;
$^1$H NMR δ 3.87 (s, 3H), 4.13 (s, 2H), 7.10-7.80 (m, 4H), 13.20 (s, 1H).

(5-(2-Furanyl)-[1,3,4]oxadiazol-2-yl)acetic acid (**4f**): yield 71%; mp 112-113 °C;
$^1$H NMR δ 4.17 (s, 2H), 6.80 (m, 1H), 7.36 (m, 1H), 8.07 (m, 1H), 13.20 (s, 1H).

(5-(2-Thienyl)-[1,3,4]oxadiazol-2-yl)acetic acid (**4g**): yield 74%; mp 115-117 °C;

$^1$H NMR δ 4.08 (s, 2H), 7.23 (m, 1H), 7.80 (m, 1H), 7.95 (m, 1H), 13.25 (s, 1H).

## Conclusions

A practical synthetic route to aryloxadiazolylacetic acids and their ethyl esters was described. The method is simple, efficient, versatile, and uses commercially available starting materials.

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