A Novel Method for the Synthesis of 2,2-Dimethyl-1,3-dioxolan-4-one, and Its Reactions with Secondary Amines

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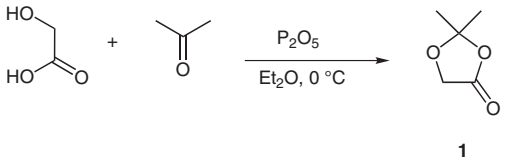
Abstract: A novel method for the synthesis of 2,2-dimethyl-1,3-dioxolan-4-one, as well as the syntheses of amides of glycolic acid via its reaction with secondary amines, is described.

Key words: amides, amines, condensation, glycolic acid, 1,3-dioxolane



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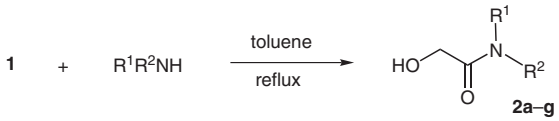
Scheme 1

Amides of glycolic acid have been found to be useful in chemistry, biochemistry and related fields. They have been utilized as herbicides[1] and peripheral benzodiazepine receptor effectors.[2] The thiasolyl derivatives have remarkable antitubercular activity[3] as well as antiallergic and antiinflammatory activity.[4] Phenoxypyridine derivatives have also been successfully used as cytoprotective agents.[5] Roxatidine has been described as an antagonist of the histamine H_2-receptor with an expressed antiulcer activity.[6]

Since direct syntheses of amides via glycolic acid and appropriate amines give, as a rule, rather low yields and glycolic acid anhydrides or halides do not exist, numerous non-trivial routes[7] have been developed for the synthesis of the amides. The most promising method is based on the degradation of 1,3-dioxolanones (acetonides) with primary amines.[8] Compared to other methods, it allows the preparation of a wide range of monoalkylamides with good yields, however, the inaccessibility of the required dioxolanes is a great disadvantage of these methods. To our knowledge, the only route to the acetonide of glycolic acid reported uses hazardous carbon disulfide and results in low (35%) yields of the desired dioxolane.[9] In this communication we report on a new, convenient synthesis of 2,2-dimethyl-1,3-dioxolan-4-one (**1**) and investigate its reactivity with secondary amines to give amides of glycolic acid. Our approach consists of the condensation of glycolic acid with acetone in the presence of phosphorus pentoxide in diethyl ether (Scheme 1).[10]

The reaction was carried out under mild conditions and the resulting 1,3-dioxolane was purified by distillation in vacuo to yield 65% of the product as a colorless liquid.

In early syntheses, 1,3-dioxolane **1** was used in reactions with primary amines in order to prepare monoalkyl amide derivatives.[8] Herein we describe the preparation of *N*,*N*-dialkylamides of glycolic acid. Amides **2a–g** have been synthesized by the reaction of 1,3-dioxolane **1** with an excess of the appropriate amine (Scheme 2).



2a $R^1 = R^2 = Et$
2b $R^1 = R^2 = n$-Pr
2c $R^1 = R^2 = n$-Bu
2d $R^1 = R^2 = n$-Hex
2e $R^1 + R^2 = -(CH_2)_5-$
2f $R^1 + R^2 = -(CH_2)_2-O-(CH_2)_2-$
2g $R^1 = Et$, $R^2 = Ph$

Scheme 2

The reactions were carried out in refluxing toluene over 10–14 hours. Analytically pure samples were obtained after distillation (**2a–e** and **g**) or recrystallization (**2f**). By this method, dialkyl amides **2a–f** could be prepared with high yields (56–93%).

A reduction of the nucleophilicity of the amine led to a significant decrease in reaction rate. Prolonged boiling of the dioxolane and *N*-ethylaniline led to only a small quantity of amide (5% on NMR spectroscopy data); however, if the reaction was carried out in the presence of catalytic amount of acid, the *N*-ethylanilamide of glycolic acid **2g** was obtained with 29% yield. This reaction was more sensitive to the influence of steric factors; the reaction of sterically hindered *N*,*N*-diisopropylamine and dioxolane did not proceed not at all.

In conclusion, we have demonstrated a novel, convenient synthesis of 2,2-dimethyl-1,3-dioxolan-4-one (**1**) and its application for the syntheses of N,N-disubstituted amides of glycolic acid (**2a–g**).

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All the reactions were carried out in freshly distilled, anhydrous solvents under moisture-free conditions. Melting points were determined on a Boetius apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ at 298 K on a Varian VXR-300 instrument at 300 MHz and all shifts are referenced to TMS.

2,2-Dimethyl-1,3-dioxolan-4-one (1)
A suspension of phosphorus pentoxide (40 g, 0.28 mol) in Et_2O (100 mL) was cooled to –18 °C and an ice-cold solution of glycolic acid (10 g, 0.13 mol) in acetone (50 mL) was added dropwise with efficient stirring. When the phosphorus pentoxide formed a lump, it was kneaded with a spatula. The resulting solution was filtered and the solvents were removed in vacuo to give an oil that was distilled under reduced pressure to give **1**.

Yield: 9.96 g (65.2%); colorless liquid; bp 49–50 °C/15 mmHg (Lit.[15] 41 °C/11 mmHg).

^{1}H NMR ($CDCl_3$): δ = 4.34 (s, 2 H, CH_2), 1.59 (s, 6 H, CH_3).

Syntheses of Amides 2a–g; General Procedure
A solution of amine (70 mmol) and dioxolane (35 mmol) in toluene (60 mL) was refluxed for 14 h. After cooling, solvent and excess of amine was removed under reduced pressure and the resulting amides were distilled in vacuo for compounds **2a–e** and **2g**, or recrystallized (**2f**).

***N*,*N*-Diethyl-2-hydroxyacetamide (2a)**
Yield: 72%; bp 64–65 °C/0.08 mmHg (Lit.[7a] 119–124 °C/17 mmHg).

^{1}H NMR ($CDCl_3$): δ = 4.15 (s, 2 H, CH_2O), 3.43 (br s and q, 3 H, OH and NCH_2), 3.14 (q, 2 H, NCH_2), 1.16 (m, 6 H, 2 × CH_3).

***N*,*N*-Di(*n*-propyl)-2-hydroxyacetamide (2b)**
Yield: 56%; bp 123–124 °C/12 mmHg.

^{1}H NMR ($CDCl_3$): δ = 4.14 (s, 2 H, CH_2O), 3.67 (br s, 1 H, OH), 3.33 (m, 2 H, NCH_2), 3.02 (m, 2 H, NCH_2), 1.56 (m, 4 H, 2 × CH_2CH_3), 0.895 (m, 6 H, 2 × CH_3).

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.40; H, 10.94; N, 8.64.

***N*,*N*-Di(*n*-butyl)-2-hydroxyacetamide (2c)**
Yield: 72.8%; bp 82–83 °C/0.02 mmHg.

^{1}H NMR ($CDCl_3$): δ = 4.14 (s, 2 H, CH_2O), 3.71 (br s, 1 H, OH), 3.36 (t, *J* = 7.6 Hz, 2 H, NCH_2), 3.05 (t, *J* = 7.6 Hz, 2 H, NCH_2), 1.52 (m, 4 H, 2× NCH_2CH_2), 1.32 (m, 4 H, 2 × CH_2CH_3), 0.94 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.92 (t, *J* = 7.2 Hz, 3 H, CH_3).

Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 64.38; H, 11.40; N, 7.42.

***N*,*N*-Di(*n*-hexyl)-2-hydroxyacetamide (2d)**
Yield: 82.3%; bp 125–128 °C/0.02 mmHg.

^{1}H NMR ($CDCl_3$): δ = 4.13 (s, 2 H, CH_2O), 3.35 (br s, 1 H, OH), 3.35 (m, 2 H, NCH_2), 3.04 (m, 2 H, NCH_2), 1.53 (m, 4 H, 2 × NCH_2CH_2), 1.28 [m, 12 H, 2 × -$(CH_2)_3$-], 0.88 (m, 6 H, 2 × CH_3).

Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.07; H, 12.03; N, 5.75. Found: C, 69.09; H, 12.30; N, 6.02.

4-Hydroxyacetylpiperidine (2e)
Yield: 75%; bp 135–138 °C/1 mmHg (Lit.[7e] 76–80 °C/0.08 mmHg).

^{1}H NMR ($CDCl_3$): δ = 4.14 (s, 2 H, CH_2O), 3.60 (m, 2 H, NCH_2), 3.43 (br s, 1 H, OH), 3.20 (m, 2 H, NCH_2), 1.66 (m, 2 H, CH_2), 1.28 (m, 4 H, 2 × CH_2).

4-Hydroxyacetylmorpholine (2f)
Crystallized from EtOAc–hexane, 1:20.

Yield: 93.2%; mp 72–74 °C (Lit.[11] 70–72 °C).

^{1}H NMR ($CDCl_3$): δ = 4.15 (s, 2 H, CH_2O), 3.67 (m, 6 H, NCH_2 and 2 × OCH_2), 3.27 (m, 2 H, NCH_2).

***N*-Ethyl-*N*-Phenyl-2-hydroxyacetamide (2g)**
A solution of *N*-ethylaniline (46.57 g, 260 mmol), dioxolane (6.03 g, 52 mmol) and two drops of H_2SO_4, in toluene (90 mL) was refluxed for 24 h. After cooling, the solvent was removed under reduced pressure and the resulting amide was distilled in vacuo two times.

Yield: 2.75 g (29.5%); bp 126–128 °C/1 mmHg; mp 37–39 °C (Lit.[12] 39–41 °C).

^{1}H NMR ($CDCl_3$): δ = 7.42 (m, 3 H, Ph), 7.16 (m, 2 H, Ph), 4.47 (br s, 1 H, OH), 3.79 (m, 2 H, NCH_2), 3.76 (s, 2 H, OCH_2), 1.14 (t, *J* = 7.2 Hz, 3 H, CH_3).

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