Generation of Stable Synthetic Equivalents of Unstable α-Alkoxyacetaldehydes: An Improved Preparation of Dirithromycin

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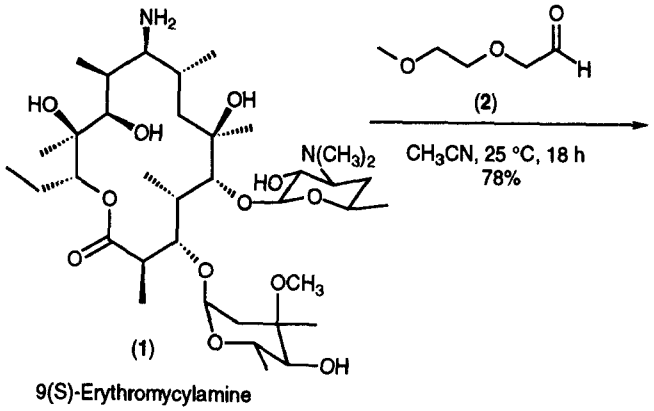
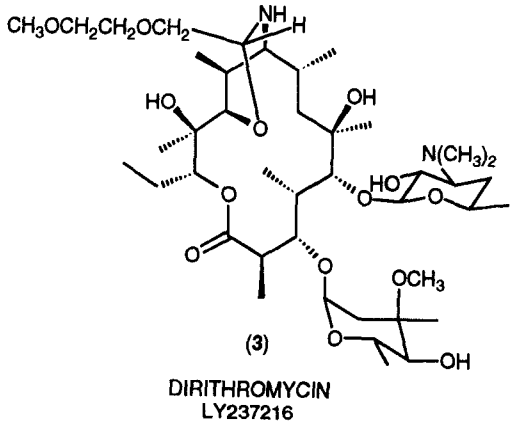
Described is the in situ preparation of the hemiacetals of α-alkoxyacetaldehydes. The hemiacetals are generated by hydrolysis of an acetal precursor in aqueous acetonitrile solutions. These hemiacetals serve as stable aldehyde equivalents, thus circumventing the production and isolation of unstable α-alkoxyaldehydes. The hemiacetal of 2-methoxyethoxyacetaldehyde is utilized in an effective and efficient preparation of Dirithromycin (LY237216).

Ether and polyether groups are often appended to potential drug substances in order to increase bioavailability. Such is the case with dirithromycin (**3**) where the 2-methoxyethoxyacetaldehyde aminal appendage aids in the delivery of the bioactive (9*S*)-erythromycylamine (**1**).[1] The aminal of dirithromycin is formed by the condensation of **1** and 2-methoxyethoxyacetaldehyde (**2**) (see Scheme 1).[2] However, low molecular weight α-alkoxyaldehydes are notoriously unstable species and 2-methoxyethoxyacetaldehyde is no exception to that trend.[3,4] Production of this unstable aldehyde is quite difficult, thus hampering the large scale production of dirithromycin. This paper describes an unusual in situ preparation of a stable yet reactive equivalent to α-alkoxyaldehydes.

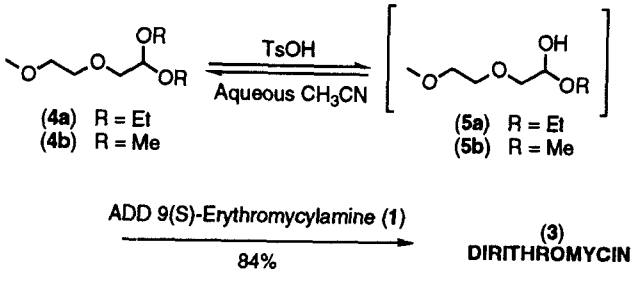




Scheme 1

Previously reported preparations of 2-methoxyethoxyacetaldehyde focused on the hydrolysis of an acetal precursor to generate the requisite aldehyde.[4,5] However, we found that generation of aldehyde **2** via such a procedure was severely hampered by incomplete hydrolysis and production of a complex mixture of products. In addition, the aldehyde readily hydrated in aqueous solutions preventing effective extraction of the product from hydrolysis reactions. The aldehyde's tendency to polymerize and decompose upon storage created handling problems, especially on multikilogram scale. Presumably, the polymerization was initiated by rapid hydrate formation. Several other methods to generate α-alkoxyacetaldehydes have been described.[6] These preparations suffer from poor yields and encounter the same isolation difficulties found with **2**. Previously, it was reported that α-alkoxyacetaldehyde **2** would not undergo simple reductive amination and therefore was of limited synthetic utility.[4] In general, the utility of these aldehydes in synthesis is limited by their stability.

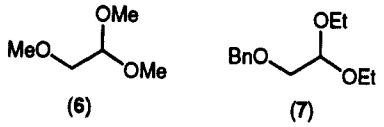
The problems associated with the production, storage and use of these unstable aldehydes can be overcome by the in situ generation of the stable hemiacetal or aldehyde equivalents. Hydrolysis of acetal **4a** under standard conditions (aq H_2SO_4, 45 °C for 6 hours with ethanol removal by vacuum distillation; or toluene, aq H_2SO_4, with azeotropic removal of ethanol) yielded only 20–30% of the requisite aldehyde **2** after distillation. However, smooth hydrolysis of this acetal to a hemiacetal was achieved under relatively mild conditions. Stirring acetal **4** in 3–10% aqueous acetonitrile (CH_3CN) with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) led to an equilibrium mixture of acetal **4** and hemiacetal **5** (Scheme 2). The presence of the requisite aldehyde could not be detected in the reaction mixture by ^1H NMR; however, formation of dirithromycin occurred upon addition of 0.5 equivalent of (9*S*)-erythromycylamine (**1**) to the equilibrium mixture (Scheme 2).[7] Presumably, the hemiacetal was consumed through rapid equilibration with the corresponding aldehyde which was known to react rapidly with **1**.[1] In fact, addition of sodium borohydride ($NaBH_4$) to the hydrolysis mixture rapidly



Scheme 2

afforded a mixture of acetal **4** and 2-(2-methoxyethoxy)-ethanol which indicates the presence of aldehyde through an equilibrium process.

Further support for the presence of the hemiacetal was gleaned by NMR analysis of hydrolysis reactions carried out in deuterated acetonitrile (CD_3CN). The structure of the hemiacetal was determined by ^1H, ^1H COSY and ^{13}C, ^1H COSY correlation techniques performed on equilibrium mixtures.[8] Additionally, hemiacetal was the hydrolysis product from reactions with the acetals of other α-alkoxyacetaldehydes such as methoxyacetaldehyde dimethyl acetal (**6**) and benzyloxyacetaldehyde diethyl acetal (**7**). This observation is thought to be general among all low molecular weight α-alkoxyacetaldehyde dialkyl acetals.



(6) (7)

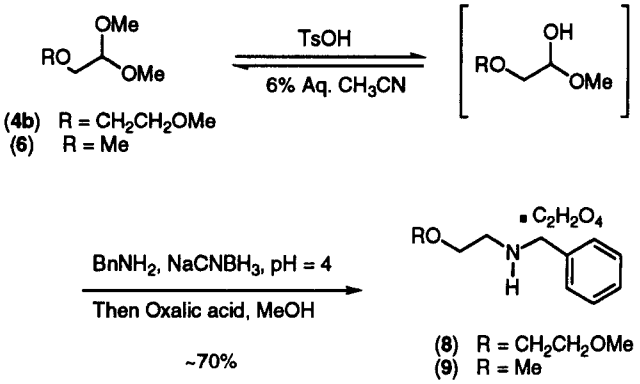
Hemiacetal formation proved to be unique to the aqueous CH_3CN solvent system. The exclusive formation of the hemiacetal was not observed in aqueous acetone, tetrahydrofuran, dimethylformamide, or dimethyl sulfoxide. Hydrolysis of these acetals in water gave complex mixtures of products which were prone to polymerization. The hydrolysis reaction in CH_3CN was catalyzed by any sulfonic acid (i.e. *p*-toluenesulfonic, methanesulfonic or camphorsulfonic) and mineral acids such as sulfuric and hydrochloric acid. Although the reaction was catalytic in acid, the amount of hemiacetal at equilibrium was dependent upon the concentration of acid. For instance, hydrolysis of acetal **4b** catalyzed by *p*-TsOH (0.06 equiv, 6% aq CH_3CN, 23 °C)[9] gave an equilibrium ratio of 2.8/1 hemiacetal/acetal, 0.04 equivalents of the acid catalyst yielded a 2/1 ratio, and 0.02 equivalents gave a 1/1 ratio.[10,11]

The hydrolysis occurred at a reasonable rate (6–8 hours at 23 °C) in 2–10% aqueous CH_3CN solutions. In general, the amount of hydrolysis seen at equilibrium increased as the amount of water in the reaction mixture was increased. For example, in 2% aqueous CH_3CN (0.04 equiv, *p*-TsOH, 23 °C, 8 h) the ratio of hemiacetal **5b**/acetal **4b** was 0.5/1, while 1/1 and 2/1 ratios were obtained from hydrolyses in 6% aqueous CH_3CN and 10% aqueous CH_3CN, respectively. However, aqueous CH_3CN solutions greater than 10% water lead to increased hydrate formation and polymerization which subsequently cause decreased aldehyde equivalency. At lower concentrations of acid, the maximum ratio of hemiacetal at equilibrium was seen in reactions containing smaller percentages of water. With 0.01 equivalent of *p*-TsOH the maximum ratio of equilibrium (1/1) was found in 6% aqueous CH_3CN, and the ratio actually decreases (0.7/1) when carried out in 10% aqueous CH_3CN solutions.[11]

The size of the alkyl group on the acetal ether also affected the hydrolysis ratio. The diethyl acetal **4a** hydrolyzed (10% aq CH_3CN, 0.04 equiv *p*-TsOH, 23 °C, 10 h) to a 2.4/1 [hemiacetal **5a**/acetal **4a**] ratio at equilibrium while under identical conditions the dimethyl acetal **4b** equilibrated to a 2.0/1 ratio.

The rate of hydrolysis and the equilibrium ratio of hemiacetal/acetal was severely affected by temperature. Hydrolysis of **4b** at ambient temperature (23 °C, 4% aq CH_3CN, 0.04 equiv *p*-TsOH) gave an equilibrium ratio of 1/1 in 8 hours. While at 33 °C, the rate increased and an equilibrium ratio of 0.9/1 was found after 5 hours. Equilibrium was achieved even faster at 40 °C (1.5 h), but the hemiacetal/acetal ratio decreased to 0.7/1. The rate of hydrolysis was also dependent on the amount of acid used to catalyze the reaction. The kinetics of this relatively simple reaction are not completely understood. However, the preceding procedure constitutes a new way to generate a stable yet reactive synthetic equivalent to α-alkoxyacetaldehyde species.

The stable hemiacetals can be used in a variety of synthetic applications. In contrast to previous reports,[4] the hemiacetal intermediates serve as stable aldehyde equivalents and undergo reductive amination in the presence of primary amines and sodium cyanoborohydride ($NaCNBH_3$). Addition of 1 equivalent of benzylamine to 2 equivalents of hemiacetals (from **4b** or **6**) generated a stable hemiaminal species which was slowly reduced by the action of $NaCNBH_3$ to afford secondary ethereal amines (**8** and **9**) in reasonable yields (Scheme 3). Since there were no alcohol products found in the reaction mixture, it was assumed that addition of the amine to the aldehyde was fast and that either conversion of hemiaminal to the imine or reduction of the imine to the secondary amine was very slow. Although this procedure was not optimized, it represents a successful methodology for generating reductive amination products from α-alkoxyaldehydes which previously could not be achieved.



Scheme 3

This novel hydrolysis procedure represents an effective method for preparing unstable α-alkoxyaldehydes in situ thus avoiding the preparation and storage of these polymerizable species. Although the aldehyde equivalents

produced by this procedure are not useful in reactions which require anhydrous conditions, the utility of this hydrolysis procedure is realized in the multikilo production of dirithromycin, where the large scale preparation and storage of the unstable 2-methoxyethoxyacetaldehyde is avoided.

(9*S*)-Erythromycylamine was obtained by the procedure described by Wildsmith.[12] 2-Methoxyacetaldehyde dimethyl acetal was obtained from Aldrich Chemical and 2-methoxyethoxyacetaldehyde dimethyl acetal was obtained from Wacker Chemical. 2-Methoxyethoxyacetaldehyde diethyl acetal and benzyloxyacetaldehyde diethyl acetal were pepared by the procedure reported by Harris[4] or the procedure reported by Beal.[5] Satisfactory microanalyses obtained: C ± 0.36, H ± 0.36, N ± 0.22.

Dirithromycin (3):
Acetal **4b** (3.0 g, 18.4 mmol) was placed in a three-neck flask equipped with a mechanical stirrer and diluted with CH_3CN (15 mL) containing 4% water by volume. *p*-TsOH (50 mg, 0.27 mmol) was added, and the mixture was stirred at ambient temperature for a minimum of 8 h. (9*S*)-Erythromycylamine **(1)** (5.0 g, 6.80 mmol) was added in portions over 15–20 minutes. After 30 min, the amine had totally dissolved. After stirring at r.t. for 10 h, the reaction mixture was cooled to 0 °C and stirred an additional 2 h. The solid was filtered, washed with cold CH_3CN, and dried to yield dirithromycin (4.75 g, 84%) as a crystalline white solid: mp 186–189 °C (decomposed). The spectral data was identical to that previously reported by Counter.[1]

General Reductive Amination Procedure:
The requisite acetal (60.9 mmol) was placed in a three-necked flask equipped with a mechanical stirrer and diluted with CH_3CN (50 mL) containing 6% water by volume. *p*-TsOH (200 mg, 1.0 mmol) was added and the mixture was stirred at r.t. for a minimum of 8 h. Benzylamine (2.7 mL, 2.68 g, 25.0 mmol) was added to the reaction mixture and the reaction mixture was stirred for 30 min. Water (10 mL) was added to the reaction mixture and the mixture was adjusted to pH ~ 4 using 10% HCl. $NaCNBH_3$ (4.14 g, 60.9 mmol) was added and the reaction mixture was acidified to pH 4 with 10% HCl. After stirring for 72 hours at r.t., the mixture was adjusted to pH 10 using dilute aqueous KOH. The reaction mixture was extracted with CH_2Cl_2 (2 × 100 mL). The CH_2Cl_2 layer was extracted with 0.1% HCl (75 mL). The aqueous layer was made basic by the dropwise addition of conc. NH_4OH. The basic aqueous layer (pH ~ 10) was extracted with CH_2Cl_2 (2 × 50 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and concentrated in vacuo. The crude secondary amine was dissolved in THF (10 mL) and a solution of oxalic acid (2.25 g, 25.0 mmol) in MeOH (10 mL) was added dropwise. The slurry was cooled to 0 °C, stirred for one h, and collected by vacuum filtration. The filtrate was washed with cold Et_2O (25 mL) and dried in vacuo at r.t. overnight.

Benzyl-2-(methoxyethoxy)ethylamine Oxalate Salt **(8)**:
Yield: 5.30 g (71%), mp 209–211 °C.

^{1}H NMR (DMSO-d_6): δ = 7.51 (m, 2H), 7.41 (m, 3H), 6.20 (br, D_2O exchange), 4.16 (s, 2H), 3.68 (t, J = 5.4 Hz, 2H), 3.54 (m, 2H), 3.46 (m, 2H), 3.25 (s, 3H), 3.05 (t, J = 5.4 Hz, 2H).

^{13}C NMR (DMSO-d_6): δ = 164.75 (s), 132.40 (s), 129.96 (d), 128.74 (d), 128.59 (d), 71.07 (t), 65.51 (t), 65.82 (t), 58.04 (q), 50.11 (t), 45.58 (t).

IR (KBr): ν = 3050, 2860, 1718, 1466 cm^{-1}.

HRMS calc. for $M^+ - C_2H_2O_4$ 210.1494, found 210.1496.

Benzyl-2-methoxyethylamine Oxalate Salt **(9)**:
Yield: 4.14 g (65%), mp 197–199 °C.

^{1}H NMR (DMSO-d_6): δ = 7.43 (m, 5H), 4.60 (br, D_2O exchange), 4.13 (s, 2H), 3.58 (t, J = 5.3 Hz, 2H), 3.28 (s, 3H), 3.04 (t, J = 5.3 Hz, 2H).

^{13}C NMR (DMSO-d_6): δ = 164.66 (s), 132.26 (s), 130.02 (d), 128.83 (d), 128.65 (d), 67.21 (t), 58.17 (q), 50.10 (t), 45.52 (t).

IR (KBr): ν = 3040, 2855, 1717, 1465 cm^{-1}.

HRMS calc. for $M^+ - C_2H_2O_4$ 166.1232, found 166.1236.

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(7) Like the condensation with 2-methoxyethoxyacetaldehyde reported in reference 1, the amine is rapidly consumed to give the kinetically favored epi-drithromycin (epimeric at the newly formed hemiaminal center). Epi-dirithromycin slowly equilibrates to thermodynamically more stable dirithromycin which crystallizes from the acetonitrile reaction mixture.

(8) The NMR data for the acetal **4b**: ^{1}H NMR (CD_3CN/D_2O): δ = 4.43 (t, J = 6.5 Hz, 1H), 3.65 (m, 2H), 3.57 (m, 2H), 3.52 (d, J = 6.5 Hz, 2H), 3.43 (s, 6H), 3.39 (s, 3H). ^{13}C NMR (CD_3CN/D_2O): δ = 103.78 (d), 72.53 (t), 71.44 (t), 71.26 (t), 58.94 (q), 54.53 (q).
The NMR data for the hemiacetal **5b**: ^{1}H NMR (CD_3CN/D_2O): δ = 4.57 (t, J = 6.6 Hz, 1H), 3.65 (m, 2H), 3.57 (m, 2H), 3.47 (dd, J = 6.5, 6.6 Hz, 2H), 3.42 (s, 6H), 3.40 (s, 3H). ^{13}C NMR (CD_3CN/D_2O): δ = 97.29 (d), 74.35 (t), 72.58 (t), 71.26 (t), 58.96 (q), 54.75 (q).

(9) The concentration of all the hydrolysis reactions reported in this paper were 1.0 M.

(10) The ratio of hemiacetal/acetal was determined by integrating the ^{1}H NMR signals for the hemiacetal proton and the acetal proton versus an internal standard.

(11) These results might indicate that the sulfonic acid is serving some role other than an acid catalyst, which should have no bearing on the equilibrium ratios. The changes in the amount of hemiacetal seen at equilibrium are most likely due to changes in the polarity of the reaction medium caused by increases or decreases in the amount of sulfonic acid.

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