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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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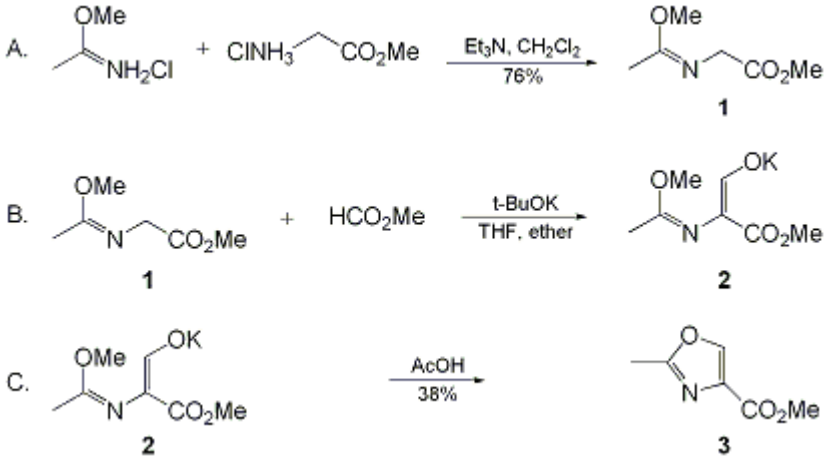
4-METHOXYCARBONYL-2-METHYL-1,3-OXAZOLE

[4-Oxazolecarboxylic acid, 2-methyl-, methyl ester]



Submitted by James D. White, Christian L. Kranemann, and Punlop Kuntiyong[1] .
Checked by Mitsuru Kitamura and Koichi Narasaka.

1. Procedure

A. Methyl α-[(methoxyethylidene)amino]acetate (**1**). A flame-dried, 500-mL, two-necked, round-bottomed flask is equipped with a stir bar, rubber septum, and an argon inlet. The flask is charged with methyl acetimidate hydrochloride (10.0 g, 91 mmol) (Note 1) and dry dichloromethane (140 mL) (Note 2). The stirred suspension is cooled to 0°C and solid methyl glycinate hydrochloride (11.5 g, 91 mmol, Note 1) is added in one portion with a powder funnel under a stream of Ar. After the mixture is stirred for 45 min at 0°C, a solution of dry triethylamine (12.7 mL, 91 mmol) (Note 2) in dry dichloromethane (11 mL) is added via syringe pump during 2.5 hr. Stirring is continued for 5 hr while the mixture is allowed to warm slowly to room temperature (Note 3). Water (30 mL, pH 7 buffered) is added, giving a clear biphasic mixture (Note 4). The phases are separated in a 250-mL separatory funnel, and the aqueous phase is extracted with dichloromethane (2 × 15 mL). The combined organic phases are washed with pH 7 buffered water (1 × 17 mL) and brine (1 × 17 mL). After the organic solution is dried over anhydrous magnesium sulfate , it is filtered and concentrated under reduced pressure, leaving 11.50 g of the crude product as a colorless solid. Distillation of this material (41 mm, 135°C) gives 10.10 g (76%) of pure methyl α-[(methoxyethylidene)amino]acetate (**1**, Note 5).

B. Potassium methyl α-[(methoxyethylidene)amino]-β-hydroxyacrylate (**2**). A flame-dried, 2-L, three-necked, round-bottomed flask is equipped with a stir bar, rubber septum, and an argon inlet. The flask is charged with a solution of potassium tert-butoxide (7.81 g, 70 mmol) (Note 1) in dry tetrahydrofuran (THF, 200 mL) (Note 2), and the solution is stirred at −10°C for 15 min. A solution of methyl α-[(methoxyethylidene)amino]acetate (10.10 g, 70 mmol) and methyl formate (5.0 mL, 84 mmol) (Note 1) in dry THF (50 mL) is added via a syringe pump during 20 min. After a further 5 min at −10°C, dry diethyl ether (750 mL) (Note 2) is added via a cannula, resulting in the formation of a yellowish precipitate. Stirring is continued for 2 hr at 0°C and the cold solution is filtered through a Schlenk tube (Note 6) under argon. The pale yellow filter cake is washed under argon with dry diethyl ether (3 × 40 mL), and the cake is dried under an argon stream and then under reduced pressure. The solid is transferred from the Schlenk tube to a wide mouthed vessel under an argon atmosphere. The resultant crude potassium methyl α-[(methoxyethylidene)amino-β-hydroxyacrylate (**2**) is used directly for the next step (Note 7).

C. 4-Methoxycarbonyl-2-methyl-1,3-oxazole (**3**). A flame-dried, 50-mL, two-necked, round-bottomed flask is equipped with a stir bar, reflux condenser, rubber septum, and an argon inlet. The

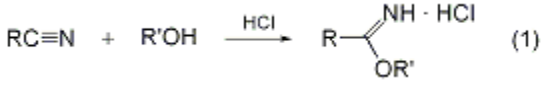
flask is charged with glacial acetic acid (15 mL) which is heated to reflux. To this is added crude potassium methyl α-[(methoxyethylidene)-amino]-β-hydroxyacrylate , prepared above, in one portion with a powder funnel. Material which adheres to the wall of the funnel and the flask is washed into the mixture with a stream of acetic anhydride . The mixture is stirred at reflux for 1.5 hr, then allowed to cool and carefully poured into a 250-mL Erlenmeyer flask containing a saturated aqueous solution of sodium bicarbonate (50 mL) (Note 7). The pH of the solution is adjusted to 8 by further addition of solid sodium bicarbonate (Note 8). The solution is extracted with dichloromethane (4 × 30 mL), and the organic extract is dried over anhydrous sodium sulfate , filtered and concentrated under reduced pressure to give 4.48 g of crude product. This is purified by distillation (41 mm, 150°C) to afford 3.74 g (38% from 1; Note 9) of 4-methoxycarbonyl-2-methyl-1,3-oxazole (**3**, Note 10).

2. Notes

1. Methyl acetimidate hydrochloride, methyl glycinate hydrochloride, potassium tert-butoxide, and methyl formate were purchased from Aldrich Chemical Company, Inc. , and were used without further purification. The checkers purchased methyl glycinate hydrochloride from Tokyo Chemical Industry Co. and potassium tert-butoxide and methyl formate from Kanto Chemical Co. Step A is very sensitive to moisture. Ethyl acetimidate hydrochloride is very hygroscopic. It must be dried before use in a desiccator over phosphorus pentoxide (P_2O_5) under reduced pressure and handled under argon.
2. Dichloromethane and triethylamine were freshly distilled from calcium hydride under argon before use. THF and diethyl ether were distilled from sodium and benzophenone under argon. The checkers used THF and diethyl ether as received from Kanto Chemical Co. (reagent grade, <0.005% water).
3. After 2 hr the ice-bath is no longer refilled with fresh ice, allowing the mixture to warm to room temperature during the remaining 3 hr.
4. Stirring for 2 to 3 min is required for complete dissolution of all precipitate.
5. The product is characterized by NMR spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.86 (s, 3 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 4.03 (s, 2 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 50.6, 51.4, 52.2, 164.8, 171.1 .
6. Compound **2** is very hygroscopic. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.60 (s, 3 H), 3.36 (s, 3 H), 3.49 (s, 3 H), 8.57 (s, 1 H) .
7. *Caution: a large amount of carbon dioxide is liberated!*
8. Water (50 mL) is added to keep all inorganic salts dissolved.
9. The submitters found that the yield of **3** can be increased to 58% if crude **2**, obtained in step B by rotary evaporation of the solvent (rather than filtration through a Schlenk tube followed by washing with ether), is taken directly into hot glacial acetic acid in step C. This procedure minimizes exposure of hygroscopic **2** to moisture. These changes were not checked.
10. The product is characterized by NMR-spectroscopy: ^{1}H NMR (400 MHz, ($CDCl_3$) δ: 2.31 (s, 3 H), 3.70 (s, 3 H), 7.97 (s, 1 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.5, 51.8, 133.0, 143.6, 161.4, 162.2 .

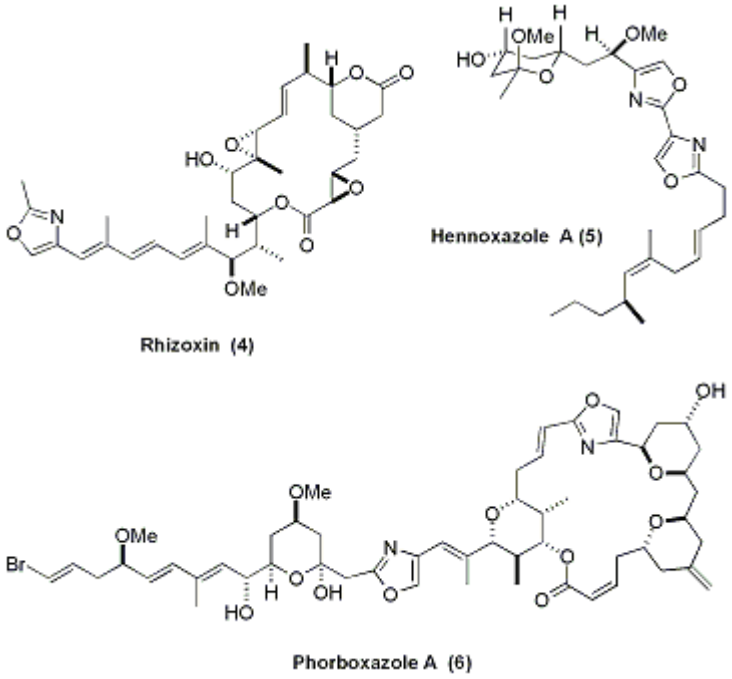
3. Discussion

The method described for the preparation of 4-methoxycarbonyl-2-methyl-1,3-oxazole is that of Cornforth,[2] and is widely applicable to the synthesis of 2-substituted 1,3-oxazole-4-carboxylates.[3] The appropriate imidate hydrochloride required for step A is obtained from the reaction of a nitrile with an alcohol in the presence of hydrochloric acid (eq. 1).[4] A different synthesis of 2-substituted 1,3-oxazole-4-carboxylates employing rhodium-catalyzed heterocycloaddition of a diazomalonate to a nitrile has been described in *Organic Syntheses* by Helquist,[5] but appears to be less general than the present route.

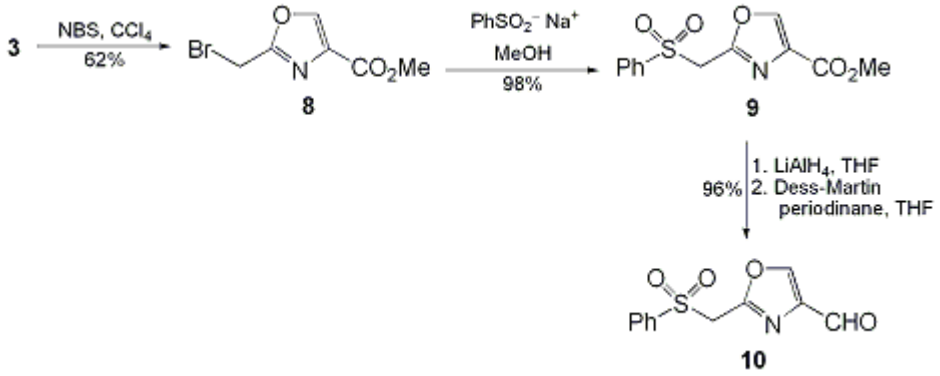


(1)

New methods for the synthesis of 2,4-disubstitued oxazoles are summarized in a recent review.[6] 2-Alkyl-1,3-oxazoles bearing alkyl, aryl, or acyl substitution at C4 are common substructures in natural products.[7] Examples include macrolides such as rhizoxin (**4**),[8] hennoxazole A (**5**),[9] and phorboxazole A (**6**),[10] as well as many cyclic peptides that incorporate an oxazole subunit presumably derived from serine.[11]



4-Methoxycarbonyl-2-methyl-1,3-oxazole (**3**) is metalated exclusively at C5 with n-butyllithium .[3] Selective functionalization at the methyl group of **3** can be achieved with N-bromosuccinimide to yield the 2-bromomethyl derivative **8**. The latter affords a route to 2,4-disubstituted oxazoles that are not immediately accessible through the Cornforth synthesis. Thus, **8** undergoes displacement with sodium phenylsulfinate to give sulfone **9**, which can then be transformed to aldehyde **10**.



References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Methoxycarbonyl-2-methyl-1,3-oxazole:
4-Oxazolecarboxylic acid, 2-methyl-, methyl ester (11); (85806-67-3)

Methyl α-[(methoxyethylidene)amino]acetate:
Glycine, N-(1-methoxyethylidene)-, methyl ester (10); (64991-38-4)

Methyl acetimidate hydrochloride:
Acetimidic acid, methyl ester, hydrochloride (8);
Ethanimidic acid, methyl ester, hydrochloride (9); (14777-27-6)

Methyl glycinate hydrochloride: ALDRICH:
Glycine methyl ester hydrochloride:
Glycine, methyl ester, hydrochloride (8,9); (5680-79-5)

Triethylamine (8);
Ethanamine, N,N-diethyl- (9); (121-44-8)

Potassium methyl α-[(methoxyethylidene)amino]-β-hydroxyacrylate:
Propanoic acid, 2-[(1-methoxyethylidene)amino]-3-oxo-, methyl ester, ion(1−), potassium (11); (105205-36-5)

Potassium tert-butoxide:
tert-Butyl alcohol, potassium salt (8);
2-Propanol, 2-methyl-, potassium salt (9); (865-47-4)

Methyl formate:
Formic acid, methyl ester (8,9); (107-31-3)

Acetic acid (8,9); (64-19-7)

Acetic anhydride (8);
Acetic acid, anhydride (9); (108-24-7)