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One-pot synthesis of oxime ethers from cinnamaldehyde or crotonaldehyde, hydroxylamine salt, potasium carbonate and alkyl halides

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ABSTRACT

Oxime ethers were synthesised in a one-pot reaction from cinnamaldehyde and crotonaldehyde, hydroxylamine hydrochloride, methyl and ethyl bromide and anhydrous potassium carbonate in THF. The reactions were completed in about 1 hour with yields of 75 to 82%.H-NMR, C-13 NMR and Infra red spectra of the products confirmed the structures of the α, β-unsaturated aldoxime ethers.

Key words: Cinnamaldehyde, crotonaldehyde, Oxime ethers, One-pot synthesis, Potasium carbonate,

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INTRODUCTION

The importance of oxime ethers in medicine, agriculture and organic synthesis is well established in literature [1-5]. The usual method for the preparation of oxime ethers involves a two-step reaction in which the first step is the reaction of aldehyde or ketone with hydroxylamine in the presence of a base to give aldoximes or ketoximes which are subsequently, in the second step, reacted with alkyl halides in the presence of a base such as sodium alkoxides, NaH, K_2CO_3, KOH, $NaHCO_3$ etc [1, 3], in solvents like acetone, DMSO, DMF *etc* to give the corresponding oxime ethers. Some authors [5] have reported a one-pot synthesis of oxime ethers from benzaldehyde or acetophenone, hydroxylamine hydrochloride, potassium hydroxide and alkyl halides in DMSO or DMF. In this report we have substituted potassium hydroxide with anhydrous potassium carbonate in an attempt to increase the yield of products using milder reaction conditions and used crotonaldehyde and ciaanamaldyhde as the carbonyl compounds. We present a one-pot procedure in which α, β-unsaturated oximes are generated from cinnamaldehyde or crotonaldehyde and coupled with alkyl halides in one pot with anhydrous potassium carbonate as base in THF.

EXPERIMENTAL SECTION

General

The infrared spectra were recorded on Perkin-Elmer Model 1310 spectrophotometer. The ^{1}Hand ^{13}C-NMR spectra of **a** and **b** were run at 250 MHz while ^{1}H, ^{13}C, ^{13}C-DEPT, ^{1}H-^{1}H coupling correlation, ^{1}H- ^{13}C ^{1}J correlations were run at 400 MHz for products **c** and **d,** the *O*-alkyl cinnamaldoxime ethers, using deuterated chloroform (or carbontetrachloride) in some cases as solvent and tetramethylsilane (TMS) as internal standard and the chemical shifts are given on the δ (ppm) scale. Elemental analysis was determined on a Yanaco CHN Corder Elemental analyzer. Cinnamaldehyde, crotonaldehyde, and hydroxylamine hydrochloride were purchased from Aldrich. Column chromatography was performed using silica gel 60 (230–400 mesh, Merck). All the oxime ethers were purified by redistillation under reduced pressure. All liquid chemical compounds used were redistilled before use but all solid reagents were used with melting points uncorrected.

Typical procedure for preparation of oxime ethers:
Excess anhydrous Potassium carbonate (5.6 mMol) was added to a mixture of hydroxyl amine hydrochloride (3.60 mMol), redistilled cinnamaldehyde (3.60 mMol) ethyl bromide (3.60 mMol) in redistilled THF (100mL). The resulting mixture was allowed to stir for fifty minutes or one hour. The reaction was monitored by TLC and the mixture was allowed to cool to room temperature and poured into cold water (100mL). The product is extracted from the mixture trice with 25mL of chloroform, washed once with water and the chloroform evaporated off under vacuum and the oxime ether is purified by vacuum distillation.

3-Phenylpropenal o-ethyl oxime (**a**)
Excess anhydrous Potasium carbonate (19.0g, 0.142 mol) was added to a mixture of hydroxyl amine hydrochloride (4.93g, 0.071 mol), redistilled cinnamaldehyde (9.43g, 0.071 mol), ethyl bromide (7.74g, 0.071mol) in redistilled THF (140 mL). The resulting mixture was allowed to reflux for fifty minutes. The reaction was monitored by TLC and the mixture was allowed to cool to room temperature and poured into cold water (160 mL). The product was extracted from the mixture trice with 50 mL of chloroform, the combined extracts was washed once with water and the chloroform evaporated off from under vacuum and the oxime ether is purified by vacuum distillation obtain colourless oil, 9.0g, 72%.

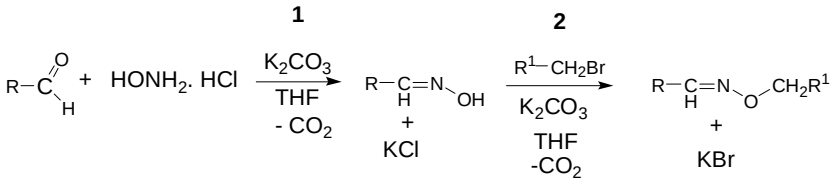
N-Methoxy-4-phenyl-1-azabutadiene or *3-Phenylpropenal O-methyl oxime ether* (b)
Excess anhydrous Potasium carbonate (19.0g, 0.142 mol) was added to a mixture of hydroxyl amine hydrochloride (4.93g, 0.071 mol), redistilled cinnamaldehyde (9.43g, 0.071 mol), methyl iodide (10.10g, 0.071 mol) in redistilled THF (150 mL). The resulting mixture was allowed to reflux for fifty minutes. The reaction was monitored by TLC and the mixture was allowed to cool to room temperature and poured into cold water (150 mL). The product was extracted from the mixture trice with 50 mL of chloroform each time, the combined extracts was washed once with water and the chloroform evaporated off from the mixture under vacuum and the oxime ether is purified by vacuum distillation to obtain an oily liquid. 7.50g (65%).

But-2-enal O-methyl oxime (**c**).
Excess anhydrous Potasium carbonate (19.0g, 0.142 mol) was added to a mixture of hydroxyl amine hydrochloride (4.93g, 0.071 mol), redistilled crotonaldehyde (4.98g, 0.071mol), methyl iodide (10.1g, 0.071 mol) in redistilled THF (160 mL). The resulting mixture was allowed to reflux for fifty minutes. The reaction was monitored by TLC and the mixture was allowed to cool to room temperature and poured into cold water (150 mL). The product was extracted from the mixture trice with 50 mL of chloroform, the combined extracts was washed once with water and the chloroform evaporated off under vacuum. The oxime ether was purified by vacuum distillation, (4.8g, 68.0%).

But-2-enal O-ethyl oxime (**d**).
Excess anhydrous Potasium carbonate (19.0g, 0.142mol) was added to a mixture of hydroxyl amine hydrochloride (4.93g, 0.071mol), redistilled crotonaldehyde (4.98g, 0.071mol), ethyl bromide (7.74g, 0.071mol) in redistilled THF (160 mL). The resulting mixture was allowed to reflux for fifty minutes. The reaction was monitored by TLC and the mixture was allowed to cool to room temperature and poured into cold water (150 mL). The product was extracted from the mixture trice with 50 mL portions of chloroform, the combined extracts was washed once with water and the chloroform evaporated off under vacuum. The oxime ether was purified by vacuum distillation to obtain an oily liquid (5.36g, 67%)

RESULTS AND DISCUSSION

The reactions were carried out by adding 2.5 equivalents of potassium carbonate to the aldehyde, hydroxylamine hydrochloride and ethyl bromide in THF (100mL) and the resulting mixture stirred. The products **a-d**were passed through a column of silica gel with ethyl acetate/hexane (1:2) mixture (as eluent) to eliminate traces of nitrone and other impurities. The reactions were completed within 50 minutes to one and a half hours.



R	R^1	Yield (%)
$C_6H_6CH=CH$	H	83
$C_6H_6CH=C$	CH_3	81
$CH_3CH=CH$	H	70
$CH_3CH=CH$	CH_3	76

Scheme 1

It is easy to monitor and confirm the transformations as the reaction proceeds from the aldehydes through the oximes to the corresponding oxime ethers. The absence of the C=O band of the carbonyl compounds (Cinnamaldehyde and crotonaldehyde) and the existence of a broad =N-OH band centred around 3166 cm^{-1} in the IR spectrum of the oximes is the evidence the aldehydes were transformed into the oximes. The –OH proton appears as a broad singlet at around 13.0 ppm in the ^{1}H-NMR spectrum. This peak disappears upon alkylation of the oxime.

3-Phenylpropenal o-ethyl oxime (**a**)
Colourless oil, b.p.: 100-102 ºC (10 mmHg), 8.9 mL (72%), d 0.994g/mL, IR(cm^{-1} , neat): 2820-2920, 1613(C=N), 1030 (N-O); ^{1}H-nmr (CDCl3): δ 1.25 (t, *J* = 12.5Hz, 3H, Me), 4.05-4.20(q, *J* = 12.5Hz,2H, CH2O), 6.7-6.8 (m, 2H, CH=CH), 7.1-7.4 (m, 5H, ArH), 7.8 (d, *J* = 12.5Hz, 1H, N=CH).^{13}C-nmr (CDCl3):δ 150.5,138.0, 136.0,129.0, 127.5,127.0,122.0, 70.0, 16.0. Anal. Calc. (%) forC11H13NO: C, 75.40; H, 7.48; N, 7.99; O, 9.13. Found: C, 75.60; H, 7.20, N, 7.54; O, 9.20.

N-Methoxy-4-phenyl-1-azabutadiene or *3-Phenylpropenal O-methyl oxime ether* (**b**)
Oil, b.p. 103 ºC (10 mmHg), Yield: 7.5g (65%), *d* 0.994g/mL, IR (cm^{-1} , neat): 2820-2920, 1613, 1030; ^{1}H-nmr ($CDCl_3$): δ 4.1 (s, 3H, MeO), 6.8-6.9 (m, 2H, CH=CH), 7.3-7.5(m, 5H, Ar-H), 7.9 (d, *J* = 10.0Hz, 1H, N=CH). ^{13}C-nmr ($CDCl_3$): δ 150.5, 140.0, 138.5, 129.0, 128.0, 127.0, 122.0, 63.0. Anal Calc. (%) for C10H11NO: C, 74.51; H, 6.88; N, 8.69; O, 9.93. Found: C, 74.20; H, 6.99; N, 8.88; O, 9.61.

But-2-enal O-methyl oxime (**c**).
Oil, b. p. 103 ºC (10 mmHg), d 0.894g/mL,Yield: 4.8g, 68.0%; IR (cm^{-1} , neat): 2820-2920, 1613 (C=N), 1030; ^{1}H-NMR (CDCl3): δ 1.4-1.6 (dd, *J*1 = 7Hz, *J*2 = 1Hz, 3H, Me); 4.0 (s, 3H, MeO-) 5.4-5.9 (m, 2H, CH=CH); 7.9 (d, *J* = 7Hz, 1H, N=CH); 13C-NMR (CDCl3) δ 163.0, 137.0, 124.0, 55.0, 17.0; Anal. Calc (%) for C5H9NO: C, 60.58; H, 9.15; N, 14.13, O, 16.14. Found: C, 60.42; H, 9.11; N, 14.08; O, 16.50[6].

But-2-enal O-ethyl oxime (**d**).
Oil, b.p. 107-110 ºC (12 mmHg); Yield: 5.36g, 67%, d 0.901g/mL; IR (cm^{-1}): 2820-2920, 1613, 1030; ^{1}H-NMR (CDCl3): δ 1.4-1.6 (m, 6H, Me); 4.1, (q, *J* = 8Hz, 2H, CH2O); 5.5-5.8 (m, 2H, CH=CH); 7.9 (d, *J* = 7Hz, 1H, N=CH); ^{13}C-NMR (CDCl3) δ164.0, 137.0, 124.0, 64.0, 17.0, 12.0. Anal. Calc. (%) for C6H11NO: C, 63.68; H, 9.80; N, 12.38; O, 14.14. Found: C, 63.40; H, 9.30; N, 12.20; O, 14.10[6].

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