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Convenient and Efficient Triton B–Mediated Synthesis of Functionalized Oxime Ethers

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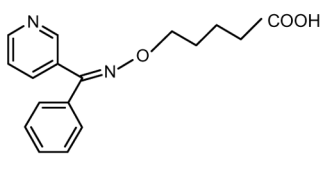
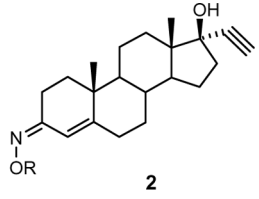
Abstract: Mild and efficient Triton B–catalyzed Michael addition of oximes to electron-deficient alkenes is described. This convenient methodology allows for the preparation of a variety of functionalized oxime ethers in high yield.

Keywords: Acrylonitrile, methyl acrylate, oxime, oxime ethers, Triton B (quaternary ammonium hydroxide salt)

Oxime ethers are important in organic synthesis[1] and also in pharmaceuticals (I).[2] Steroidal oxime ethers are also known to inhibit aromatization in breast cancer therapy.[3]





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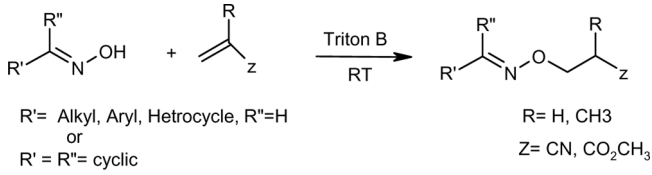
A classical method for installing this functionality is the base-catalyzed reaction of oximes with alkyl halides.[4] However, such strategies have the drawback of using lachrymatric halides and corrosive bases. Recently, oxime ethers have been prepared based on allylic substitution using palladium as the catalyst.[5] However, varieties of catalysts such as indium(III) bromide,[6] fluorapalite,[7] and indium(III) chloride[8] are known to perform Michael addition. Although these methods provide good yields, they have the drawback of using a metal catalyst, which generates metal-ion-containing waste. Moreover, tedious workup and harsh reaction conditions also prevent these methods from general applications in the context of green chemistry, so there is a need to devise an alternative protocol without metallic base or catalyst.

TritonB is a nonmetallic organic base. TritonB is known to act as an additive in organic reactions, such as epoxidation.[9] However, recent reports reveal the use of TritonB as an efficient and nonmetallic base for alkynyation,[10] Michael-type addition,[11] nitro aldol condensation,[12] and carbamate formation.[13] Because of our involvement in the development of nonmetallic reagents[14] herein we report the results of Triton B–mediated synthesis of functionalized oxime ethers by Michael-type addition (Scheme 1).

The Michael addition of cyclohexanone oxime (1 mmol) to methyl acrylate (1.5 mmol) was examined in the presence of different ratios of Triton B (1 eq., 1.5 eq., 2 eq., and 3 eq.) at room temperature. Among these, the use of 1.5 eq. of Triton B was found to be the most effective to afford cyclohexanone oxime ether (entry **d**) in 95% yield. The yield of **1a** was decreased when 1 eq. of methyl acrylate was used.

However, the rate of the reaction can be enhanced by the addition of more equivalents of Triton B. When the reaction of cyclohexanone oxime and methyl acrylate was performed with 3 eq. of Triton B, the expected oxime ether **1a** was obtained in qualitative yield in 2 h. Under optimized conditions,[15] various substituted aryl oximes (entries **f** to **n**) having electron donating and electron-withdrawing substituents were found to give the corresponding oxime ethers in good yield.



Scheme 1.

It was noticed that electron-withdrawing substituents enhance the rate of reaction. Reaction of nitro benzaldoxime (entry **l**) with methyl acrylate was accomplished in a very short time (40 min), and thiophine 2-carboaldoxime and pyridine 2-carboaldoxime react smoothly with methyl acrylate, giving the corresponding oxime ethers in high yield.

Apart from aliphatic and aromatic oximes, hetero aryl oximes (entries **f** to **j**) also underwent a smootheaction leading to the corresponding oxime ether product in high yield.

The efficiency of the procedure was further strengthened by the successful conversion of camphor oxime (entry **o**) and cholestananone oxime (entry **q**) into the corresponding oxime ethers. From Table 1, it can be observed that addition of oximes to methyl-ubstituted electron-deficient alkenes decreases the rate of reaction. For example, Michael addition of cyclohexanoneoxime (entry **e**) and pyridine 2-carboxaldoxime (entry **j**) to methylmethacrylate requires a longer reaction time for the completion of the reaction.

The present procedure is compatible with a variety of functional groups such as ester and nitrile, which give further scope to build more diverse oxime ethers.

EXPERIMENTAL

General Experimental Procedure

A mixture of oxime (1 mmol), acrylonitrile or methylacrylate (1.5 mmol), and Triton B (2 ml) were stirred at room temperature for a stipulated time (see Table 1). The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, it was extracted with solvent ether (3×10 ml).

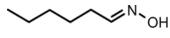
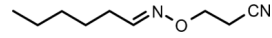
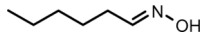
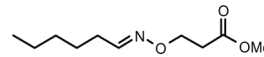
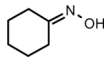
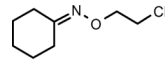
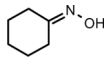
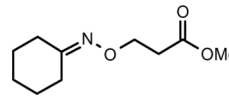
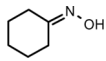
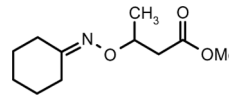
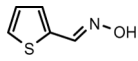
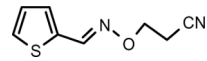
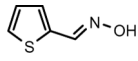
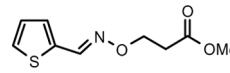
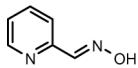
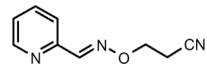
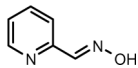
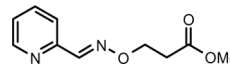
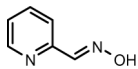
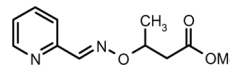
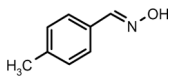
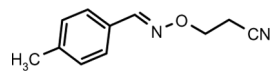
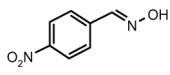
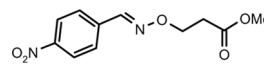
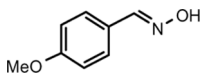
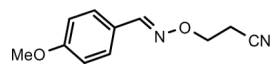
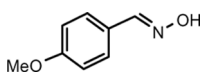
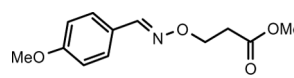
The combined ether extract was washed with water and dried over anhydrous sodium sulphate, and the solvent was removed under vacuum. The residue was purified through a small pad of silica gel using hexane–ethyl acetate (9:1).

Spectral Data for Selected Products

Compound **a**

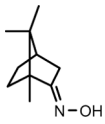
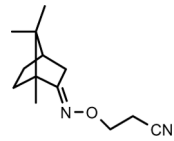
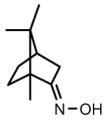
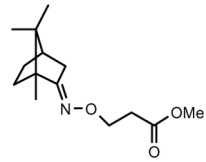
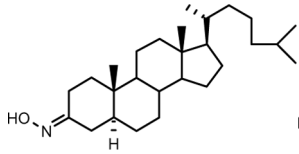
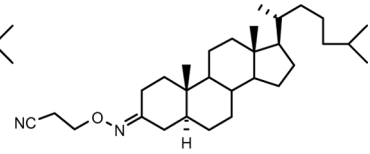
Liquid, IR (KBr): υ 3415, 2932, 2252, 1740, 1637, 1455, 1376, 1263, 1195, 1084, 1056, 885, 602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (t, 1H, $J = 6.0$ Hz), 4.22 (t, 2H, $J = 6.0$ Hz), 2.62 (t, 2H, $J = 6.8$ Hz), 2.19–2.11

Table 1.

Entry	Oximes	Product[a]	Time (min)	Yield (%)[b]
a			45	89
b			50	87
c			40	90
d			50	88
e			5.0 (h)	77
f			40	89
g			45	87
h			30	91
i			40	89
j			4.0 (h)	77
k			45	90
l			15	94
m			50	87
n			50	86

(*Continued*)

Table 1. Continued

Entry	Oximes	Product[a]	Time (min)	Yield (%)[b]
o			45	90
p			55	87
q			40	89

[a]All products were characterized by NMR, IR, and mass spectroscopy.
[b]Isolated yields after purification.

(m, 2H), 1.53–1.43 (m, 2H), 1.36–1.27 (m, 4H), 0.91 (t, 3H, $J = 6.798$ Hz); EIMS mass: m/z: 168 M^+, 155, 141, 129, 103, 82, 75, 57, 43.

Compound **d**

Liquid. IR (KBr): υ 3416, 2935, 2923, 1742, 1639, 1438, 1383, 1257, 1176, 1046, 916, 838, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.17 (t, 2H, $J = 6.1$ Hz), 3.61 (s, 3H), 2.58 (t, 2H, $J = 6.1$ Hz), 2.36 (t, 2H, $J = 6.9$ Hz), 2.12 (t, 2H, $J = 6.9$ Hz), 1.67–1.50 (m, 6H); EIMS mass: m/z: 199 M^+, 113, 103, 96, 82, 71, 75, 59, 55, 41.

Compound **j**

Liquid. IR (KBr): υ 3416, 2944, 1737, 1586, 1463, 1378, 1261, 1203, 1046, 950, 777, 516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.57 (d, 1H, $J = 5.2$ Hz) 8.11 (s, 1H), 7.80 (d, 1H, $J = 7.8$ Hz), 7.66 (dt, 1H, $J = 1.7$, 7.8 Hz), 7.26 (dd, 1H, $J = 1.7$, 5.2 Hz), 4.41, 4.19 (dd, 2H, $J = 6.9$, 11.3 Hz), 3.70 (s, 3H), 3.02–2.84 (m, 1H), 1.24 (d, 3H, $J = 6.9$ Hz); EIMS mass: m/z: 222 M^+, 191, 165, 133, 123, 107, 92, 85, 79, 78, 63, 58, 57, 51, 43.

Compound **n**

Liquid. IR (KBr): υ 3415, 2957, 2840, 1729, 1608, 1513, 1463, 1348, 1305, 1251, 1171, 1058, 1030, 954, 833, 580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.47 (d, 2H, $J = 8.9$ Hz), 6.85 (d, 2H, $J = 8.9$ Hz), 4.38 (t, 2H, $J = 6.6$ Hz), 3.81 (s, 3H), 3.70 (s, 3H), 2.71 (t, 2H, $J = 6.6$ Hz); EIMS mass: m/z: 237 M^+, 206, 151, 134, 107, 93, 77, 71, 59, 43.

Compound **p**

Liquid. IR (KBr): υ 3413, 2963, 2251, 1667, 1454, 1378, 1275, 1196, 1118, 1046, 890, 826, 536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.23 (t, 2H, $J = 6.1$ Hz), 3.7 (s, 3H), 2.6 (t, 2H, $J = 6.1$ Hz), 2.44 (m, 1H), 1.90–1.80 (m, 2H), 1.76–1.31 (m, 4H), 0.97 (s, 3H), 0.90 (s, 3H), 0.78 (s, 3H); EIMS mass: m/z: 220 M^+, 190, 175, 150, 147, 134, 122, 108, 94, 81, 69, 55, 41.

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