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A new synthetic access to *N*-alkylated nitrones through Lewis acid-catalyzed conjugate additions of aldoximes

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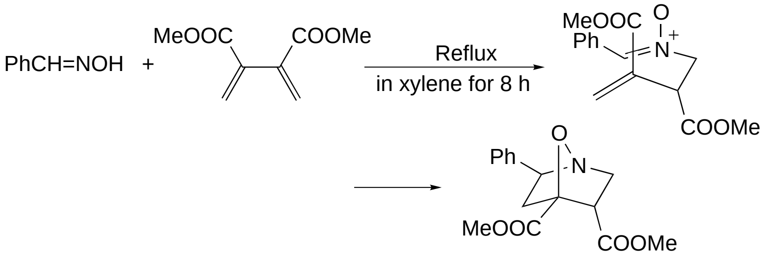
Abstract—In the presence of Lewis acid catalysts, aldoximes react with α,β-unsaturated carbonyl compounds at room temperature to give *N*-alkylnitrones in good yields. Combination of two Lewis acid catalysts, zinc(II) iodide/boron trifluoride etherate (50 mol%/50 mol%), is the best choice to mediate the reactions producing *N*-alkylated nitrones in excellent yields. In this procedure, a variety of aldoximes and α,β-unsaturated carbonyl acceptors can be employed. © 2001 Elsevier Science Ltd. All rights reserved.

Nitrone generation by reaction of oximes with a variety of alkylating agents offers one of the most convenient nitrone generation methods.[1–7] In 1988, Grigg and co-workers discovered a new reaction, now known as Grigg's nitrone generation, which involves the *N*-alkylation of oximes through conjugate additions to electron-deficient alkenes to produce nitrone 1,3-dipoles (nitrone formation step).[7] The resulting nitrone intermediates, under the reaction conditions, further undergo 1,3-dipolar cycloaddition reactions to the same alkenes to give cycloadducts (cycloaddition step). Conjugate addition step is often slower for most of electron-deficient alkenes than the subsequent cycloaddition step under heating conditions. Therefore, cycloadducts instead of nitrones are usually produced in the Grigg reaction, indicating that this method can not be a highly powerful synthetic route to nitrones. When an α,β-unsaturated carbonyl acceptor can be activated by coordination to a Lewis acid catalyst, rate acceleration of the nitrone formation step is expected.[8] Although the subsequent cycloaddition step of the resulting nitrone is also possible to be accelerated,[9] this Lewis acid-catalyzed nitrone cycloaddition is not so easy. Accordingly, there is an opportunity to open a new entry to the synthetic route to nitrones by the Lewis acid-catalyzed activation of reactions between oximes and α,β-unsaturated carbonyl acceptors. However, the Lewis acid-catalyzed versions of the Grigg reaction have remained unsuccessful for the isolation of the intermediary nitrones.[8] We would like to present in this communication the convenient synthetic access to *N*-alkylnitrones from aldoximes and α,β-unsaturated carbonyl compounds in the presence of Lewis acid catalysts.



Keywords: nitrones; oximes; addition reaction; catalysts; enals; enones.

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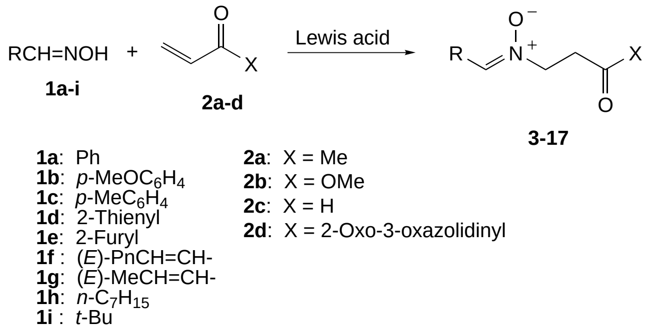


Scheme 1.

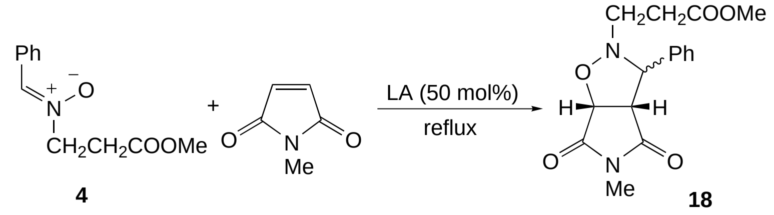
Benzaldoxime (**1a**)[10] was allowed to react with 3-acryloyl-2-oxazolidinone (**2d**) at room temperature for 24 h in dichloromethane in the presence of mixed Lewis acids such as $ZnI_2/BF_3{\cdot}OEt_2$ (50 mol%/50 mol%). The corresponding 1:1 adduct **5**, obtained in a quantitative yield, was characterized as 3-[3-(benzylideneamino)-propanoyl]-2-oxazolidinone *N*-oxide on the basis of elementary analysis as well as spectral data (Scheme 1 and Table 1).[11] The reason why 3-acryloyl-2-oxazolidinone (**2d**) was employed as acceptor in the present work is because (1) **2d** has no substituents at the β-position so that this acceptor must be most reactive for *N*-alkylation of oximes and because (2) **2d** as bidentate acceptor should be most effectively activated by a Lewis acid catalyst.

After survey for some other acceptors, it has been found that not only bidentate acceptor **2d** but also monodentate acceptors such as 3-buten-2-one (**2a**), methyl acrylate (**2b**) and acrolein (**2c**) could be successfully employed, while reactivities are quite different from each other (Table 1). The bidentate acceptor **2d** was most reactive under the catalyzed conditions as readily anticipated and the α,β-unsaturated ketone **2a** was also highly reactive. On the other hand, the acrylate ester **2b** belongs to the least reactive so that heating under reflux in benzene is necessary to complete the reaction. As to aldoximes, more reactive than benzaldoxime (**1a**) and its *p*-substituted derivatives **1b**,**c** are heteroaromatic aldoximes such as 2-thiophenecarboxaldehyde oxime (**1d**) and 2-furancarboxaldehyde oxime (**1e**). α,β-Unsaturated aldehyde oximes such as (*E*)-cinnamaldoxime (**1f**) and (*E*)-crotonaldoxime (**1g**) are especially reactive and aliphatic aldoximes **1h**,**i** are also more reactive than **1a**–**c**. Thus, a variety of *N*-alkylated

Table 1. Conjugate additions of oximes **1a**–**i** to α,β-unsaturated carbonyl compounds **2a**–**d** in the presence of $ZnI_2/BF_3{\cdot}OEt_2$ (50 mol%/50 mol%) leading to nitrones **3**–**17**[a]

Entry	Oximes	R	Acceptors (equiv.)	X[b]	Temp. (°C)	Time (h)	Nitrone	Yield (%)
1	**1a**	Ph	**2a** (1.5)	Me	Rt	7	**3**	86
2[c]	**1a**	Ph	**2b** (2.0)	OMe	reflux	24	**4**	Quant.
3	**1a**	Ph	**2d** (1.1)	Ox	Rt	24	**5**	Quant.
4[c]	**1b**	*p*-$MeOC_6H_4$	**2b** (1.0)	OMe	Reflux	24	**6**	83
5[c]	**1c**	*p*-MeC_6H_4	**2b** (2.0)	OMe	Reflux	24	**7**	Quant.
6[c]	**1d**	2-Thienyl	**2b** (2.0)	OMe	Reflux	24	**8**	98
7	**1d**	2-Thienyl	**2d** (1.1)	Ox	Rt	24	**9**	Quant.
8[c]	**1e**	2-Furyl	**2b** (2.0)	OMe	Reflux	24	**10**	79
9	**1e**	2-Furyl	**2d** (1.1)	Ox	Rt	24	**11**	94
10	**1f**	(*E*)-PhCH=CH-	**2a** (1.0)	Me	Rt	7	**12**	99
11[c]	**1f**	(*E*)-PhCH=CH-	**2b** (1.3)	OMe	Reflux	24	**13**	86
12	**1f**	(*E*)-PhCH=CH-	**2c** (1.0)	H	Rt	6	**14**	Quant.
13	**1g**	(*E*)-MeCH=CH-	**2a** (1.0)	Me	Rt	6	**15**	Quant.
14	**1h**	*n*-C_7H_{15}	**2a** (1.5)	Me	Rt	4	**16**	Quant.
15	**1i**	*t*-Bu	**2a** (1.5)	Me	Rt	10	**17**	98

[a] Solvent: dichloromethane unless otherwise noted.
[b] Ox: 2-oxo-3-oxazolidinyl.
[c] Solvent: benzene.



LA	Solvent	Time/h	Yield/% (*endo* : *exo*)
none	Toluene	20	99 (55 / 45)
$MgBr_2{\bullet}OEt_2$	CH_2Cl_2	20	67 (65 / 35)
ZnI_2	Benzene	20	85 (48 / 52)

Scheme 2.

nitrones **3**–**17** are accessible by the above reactions. Structures of the resulting nitrones were finally confirmed by 1,3-dipolar cycloaddition reactions. One typical example is given in Scheme 2 where nitrone **4** was reacted with *N*-methylmaleimide under various conditions. Under the uncatalyzed conditions a 55:45 diastereomeric mixture of **18** was produced in a quantitative yield.

However, ketoximes such as benzophenone oxime and fluorenone oxime were totally sluggish compared with aldoximes. This decreased reactivity of ketoximes makes a sharp contrast to the Grigg's reactions in which ketoximes can be successfully applied, though their reactions had been performed under heating.[8b] Thus, the present nitrone formation reactions can be generally applied to the combinations between a variety of aldoximes and α,β-unsaturated carbonyl acceptors. Although this nitrone formation is usually too slow at room temperature without Lewis acid catalysts, it has additionally been found out that (*E*)-cinnamaldoxime (**1f**) as one of the most reactive aldoximes can react with α,β-unsaturated ketone **2a** and aldehyde **2c** without the acceleration by Lewis acid catalysts. Especially the reaction of **1f** with acrolein (**2c**) proceeds more cleanly under uncatalyzed conditions at room temperature, than the catalyzed reaction, to give the corresponding nitrone **14**.[12]

Use of the mixed Lewis acids of $ZnI_2/BF_3{\cdot}OEt_2$ is essential to attain high yields of nitrones in the present nitrone synthesis. By use of an equimolar amount of ZnI_2 (1 equiv.) as bidentate Lewis acid catalyst in the reaction of **1a** with 3-buten-2-one (**2a**), rate acceleration was observed not only in the nitrone formation step but also in the undesired dipolar cycloaddition step giving a mixture of nitrone **5** and the corresponding cycloadduct (2:1 adduct between **2a** and **1a**, Table 2). On the other hand, the reaction in the presence of an equimolar amount of $BF_3{\cdot}OEt_2$ as monodentate Lewis acid catalyst is terminated halfway to recover part of the both starting materials **1a** and **2a**. Use of the mixed Lewis acid catalysts, ZnI_2 and $BF_3{\cdot}OEt_2$ each in half an equimolar amount, effectively mediate the nitrone formation step to produce high to quantitative yields of the corresponding nitrones (Table 1). The reason why use of the mixed Lewis acid is particularly effective has remained so far unsolved. Heating has to be avoided in the reaction using acceptors other than methyl acrylate (**2b**), otherwise the nitrones formed undergo serious decomposition leading to a mixture of complex products.

Table 2. Lewis acid catalysis in the reaction between oxime **1a** and 3-buten-2-one (**2a**) at room temperature[a]

Entry	Lewis acid	Mol%	Time (h)	Yield (%) of **3**
1	ZnI_2	50	48	25
2	ZnI_2	100	7	58[b]
3	$BF_3{\cdot}OEt_2$	50	48	25
4	$BF_3{\cdot}OEt_2$	100	7	55[c]
5	$ZnI_2/BF_3{\cdot}OEt_2$	50/50	7	86

[a] Solvent: dichloromethane.

[b] Formation of the cycloadduct is accompanied.

[c] The starting materials remained unchanged.

The workup procedure to isolate the nitrones after completion of reaction is also critical; the usual aqueous workup of the reaction should be avoided. *N*-Alkylnitrones are usually polar molecules and they are quite soluble in water. Accordingly some serious weight loss of nitrones takes place when the reaction is worked up with water and purified through a long silica gel column. The following procedure is recommended: immediately after the reaction is complete (checked by TLC), the reaction mixture is filtered without aqueous workup through a short silica gel column. Usually this procedure gives almost pure nitrones. If more purification is needed, another step of chromatographic purification is repeated.

In conclusion, Lewis acid-catalyzed conjugate addition reactions between aldoximes and α,β-unsaturated carbonyl compounds at room temperature offer a convenient synthetic access leading to *N*-alkylated nitrones. Both aldoximes and α,β-unsaturated carbonyl acceptors are readily and widely available, and hence the present synthetic method can be applied to the synthesis of a variety of nitrones by combination of these substrates.

Acknowledgements

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References

1. Reviews: (a) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, Chapter 9, pp. 83–168; (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988; (c) Confalone, P. N.; Huie, E. M. *Org. React*. **1988**, *36*, 1–173.
2. Some recent methods for nitrone generation by *N*-alkylation of oximes: (a) Padwa, A.; Dent, W. H.; Schoffstall, A. M.; Yeske, P. E. *J. Org. Chem*. **1989**, *54*, 4430–4437; (b) L'abbe, G.; Bastin, L.; Dehaen, W.; Delbeke, P.; Toppet, S. *J. Chem. Soc*., *Perkin Trans. 1* **1992**, 1755–1758; (c) Dondas, H. A.; Frederickson, M.; Grigg, R.; Markandu, J.; Thornton-Pett, M. *Tetrahedron* **1997**, *53*, 14339–14354.
3. Nitrone generation by intramolecular ene reaction of oximes: (a) Armstrong, P.; Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1991**, *47*, 4495–4518; (b) Hassner, A.; Singh, S.; Sharma, R.; Maurya, R. *Tetrahedron* **1993**, *49*, 2317–2324; (c) Shindo, M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett*. **2000**, *41*, 929–932.
4. Donegan, G.; Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron Lett*. **1989**, *30*, 609–612.

5. Oxime/nitrone isomerization: (a) Grigg, R.; Heaney, F.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1991**, *47*, 4007–4030; (b) Gotoh, M.; Mizui, T.; Sun, B.; Hirayama, K.; Noguchi, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1857–1862; (c) Gotoh, M.; Sun, B.; Hirayama, K.; Noguchi, M. *Tetrahedron* **1996**, *52*, 887–900; (d) Sun, B.; Adachi, K.; Noguchi, M. *Tetrahedron* **1996**, *52*, 901–914.
6. Electrophile-mediated nitrone generation from oximes: (a) Shaw, R.; Lathbury, D.; Anderson, M.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 659–660; (b) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Marini, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1989–1994; (c) Frederickson, M.; Grigg, R.; Thornton-Pett, M.; Redpath, J. *Tetrahedron Lett.* **1997**, *38*, 7777–7780.
7. Nitrone generation and internal trapping with bifunctionalized electrophiles: (a) Grigg, R.; Malone, J. F.; Dorrity, M. R. J.; Heaney, F.; Rajviroongit, S.; Sridharan, V.; Surendrakumar, S. *Tetrahedron Lett.* **1988**, *29*, 4323–4324; (b) Grigg, R.; Dorrity, M. J.; Heaney, F.; Malone, J. F.; Rajviroongit, S.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1991**, *47*, 8297–8322; (c) Norman, B. H.; Gareau, Y.; Padwa, A. *J. Org. Chem.* **1991**, *56*, 2154–2161; (d) Yokoyama, M.; Sujino, K.; Irie, M.; Yamazaki, N.; Hiyama, T.; Yamada, N.; Togo, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2801–2809; (e) Herczegh, P.; Kovacs, I.; Szilagyi, L.; Varga, T.; Dinya, Z.; Sztaricskai, F. *Tetrahedron Lett.* **1993**, *34*, 1211–1214; (f) Frederickson, M.; Grigg, R.; Rankovic, Z.; Thornton-Pett, M.; Redpath, J.; Crossley, R. *Tetrahedron* **1995**, *51*, 6835–6852.
8. Lewis acid-catalyzed version: (a) Kusurkar, R. S.; Wadia, M. S.; Bhosale, D. K.; Tavale, S. S.; Puranik, V. G. *J. Chem. Res. (S)* **1996**, 478–479; (b) Saba, I. S.; Frederickson, M.; Grigg, R.; Dunn, P. J.; Levett, P. C. *Tetrahedron Lett.* **1997**, *38*, 6099–6102.
9. Lewis acid catalysis of nitrone cycloadditions: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–910; (b) Gothelf, K. V.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **2000**, 1449–1458.
10. *E*-Isomer of **1a** has been used.
11. 3-[3-(Benzylideneamino)propanoyl]-2-oxazolidinone *N*-oxide (**5**): Yield quant; Colorless solid; mp 169–170°C; ^{1}H NMR ($CDCl_3$): δ 3.65 (2H, t, $J=6.0$ Hz), 4.01 (2H, t, $J=8.0$ Hz), 4.33 (2H, t, $J=6.0$ Hz), 4.43 (2H, t, $J=8.0$ Hz), 7.42 (3H, m), 7.55 (1H, s), and 8.23 (2H, m); ^{13}C NMR ($CDCl_3$): δ 32.62, 42.32, 60.76, 62.27, 128.45, 128.67, 130.31, 130.51, 135.73, 153.36, and 170.68; mass m/z (rel. intensity, %) 262 (19, M^+), 245 (5), 176 (25), 107 (12), 89 (9), 77 (7), and 59 (7); IR (KBr, cm^{-1} 2360, 1782, 1762, 1695, 1423, 1400, 1382, 1365, 1346, 1276, 1217, 1191, 1145, 1120, 1043, 962, 941, 829, 758 and 692. Anal. found: C, 59.33; H, 5.44; N, 10.52; calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68%.
12. When **1f** is treated with **2c** at room temperature for 24 h in dichloromethane, the corresponding nitrone **14** was obtained in 72% yield after purification through a silica gel column chromatography.