Molecular Sieve (MS 4A) Promoted Cyclocondensation of Hindered, Aromatic Nitrile Oxides and Cyclic Diketones under Mild Conditions

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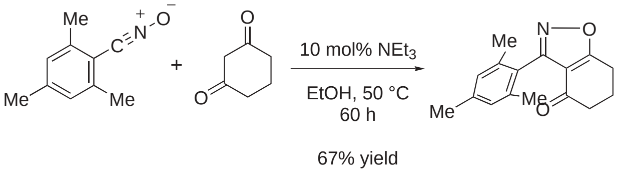
Dedicated to the memory of the late Professor Oyo Mitsunobu

Abstract: Molecular sieves (MS 4A) serve as efficient promoters for the cyclocondensation of stable, hindered nitrile oxides and a variety of cyclic diketones to afford fused isoxazoles in good yield. The operational simplicity and remarkably mild reaction conditions compliment our amine-promoted cyclocondensation conditions and demonstrate broad substrate scope.

Key words: cycloadditions, ketones, condensation, isoxazoles, molecular sieves

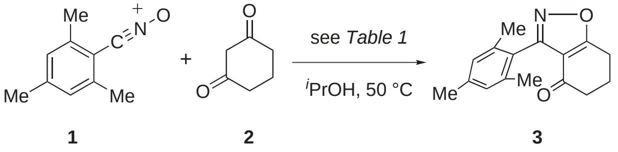
Recently, we reported the base-promoted coupling of stable aromatic nitrile oxides with cyclic diketones, affording highly functionalized fused isoxazoles in good yield.[1] Although preliminary results indicated that the reaction was catalytic with respect to the base, in practice the extended reaction times required for high yielding, catalytic cyclocondensations hampered studies towards the development of more active and enantioselective reagents (Equation 1).



Equation 1

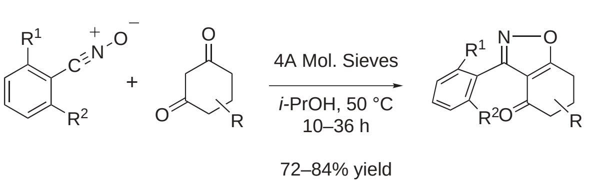
In hopes of accelerating the reaction, we sought to identify a more active amine catalyst or suitable additive with the goal of increasing the reaction rate while maintaining the mild reaction conditions. In the course of these studies, we noted that the addition of 4A molecular sieves (MS 4A) to tertiary amine catalyzed reactions resulted in a significant acceleration of the reaction rate, without an apparent increase in starting material decomposition or reaction byproducts (Table 1, entry 3). To our surprise, however, further studies revealed that molecular sieves alone, in the absence of base, effectively promoted the cyclocondensations.[2,3] Based on these observations, we now report general and exceptionally mild conditions for efficient cyclocondensations of aromatic nitrile oxides and diketones: MS 4A (1 g/mmol of nitrile oxide), *i*-PrOH, 50 °C (Equation 2).

Table 1 Optimization of MS Promoted Cyclocondensations[a]



Entry	Additive	Loading (g/mmol)	Time (h)	Yield[b] (%)
1	none	–	40	24[c]
2	10 mol% NEt_3	–	100	56
3	10 mol% NEt_3 +MS 4A	1	10	79
4	Drierite	1	180	–[d]
5	Basic alumina	1	23	62
6	MS 5A	1	72	–[d]
7	MS 13 X[e]	1	72	–[d]
8	MS 3A	1	24	66
9	MS 4A	1	9.5	78
10	MS 4A	3	5.5	81

[a] Unless otherwise indicated, all reactions were performed at 0.1 M in *i*-PrOH at 50 °C for the indicated reaction time.
[b] Yield refers to isolated yield of pure product.
[c] Nitrile oxide **1** was recovered in 54% yield.
[d] Significant amounts of nitrile oxide **1** remained at the indicated time.
[e] All molecular sieves were purchased from commercial sources in powdered form and dried prior to use.



Equation 2

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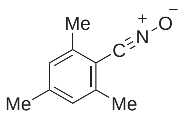
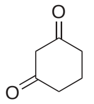
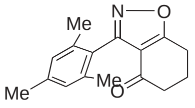
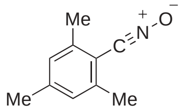
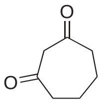
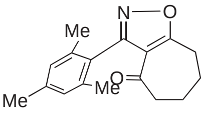
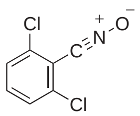
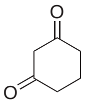
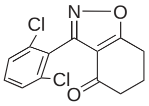
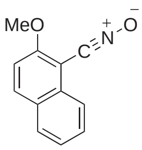
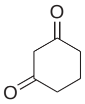
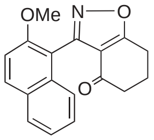
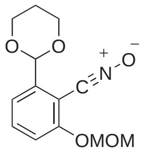
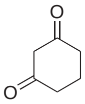
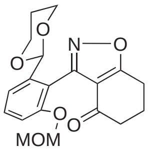
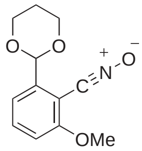
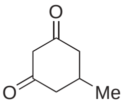
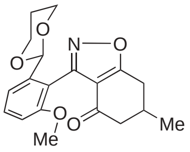
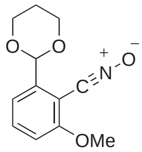
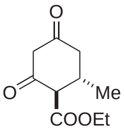
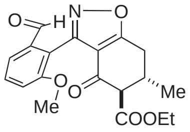
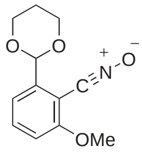
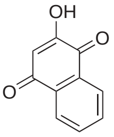
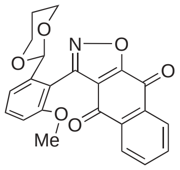
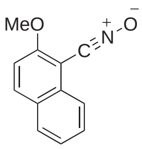
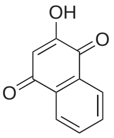
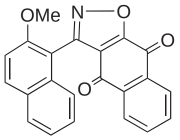
Art Id.1437-2096,E;2003,0,11,1746,1748,ftx,en;U10903ST.pdf.
DOI: 10.1055/s-2003-41436

Using stable nitrile oxide **1** and cyclic diketone **2** as model substrates, a variety of heterogeneous bases and desiccants were screened for cyclocondensation promotion to afford isoxazole **3**. While solid bases including K_2CO_3 and Na_2CO_3 proved inferior to base-promoted conditions (data not shown), a variety of solid desiccants effectively promoted the desired reaction (Table 1). A survey of commonly available reagents and molecular sieves revealed that powdered MS 3A and MS 4A promoted the cyclocondensation reaction (entries 8–10) in good yield and ac-

Table 2 Synthesis of Isoxazoles by 4A Molecular Sieve-Promoted Cyclocondensation Reactions[a]

Entry	Nitrile oxide	Compd	Ketone	Compd	Product	Compd	Time (h)	Yield[b] (%)
1		**1**		**2**		**3**	9.5	78
2		**1**		**4**		**5**	20	81
3		**6**		**2**		**7**	15	80
4		**8**		**2**		**9**	10	53
5		**10**		**2**		**11**	36	81
6		**12**		**13**		**14**	24	84
7		**12**		**15**		**16**	23	54[c]
8		**12**		**17**		**18**	12	72
9		**8**		**17**		**19**	10	53

[a] Unless otherwise indicated, all reactions were performed using 1.0 equiv nitrile oxide, 1.2 equiv diketone, and 1 g/mmol of powdered MS 4A in 0.1 M *i*-PrOH at 50 °C for the indicated time.

[b] Chemical yield of isolated, spectroscopically pure product.

[c] Combined yield for cyclocondensation and acetal deprotection based on **12**. Small amounts of stereo- and/or regioisomers were observed prior to purification by precipitation.

ceptable reaction times.[4] In contrast, molecular sieves with a larger cavity size were ineffective (entries 6, 7). Although cyclocondensation reactions occurred in the presence of basic alumina, it offered no advantages to either the molecular sieve or amine-promoted conditions (entry 5).

The use of MS 4A to promote the cyclocondensation is notable for both the mildness of the reaction conditions and its operational simplicity. Neither strongly basic nor Lewis acidic reagents are required for effective isoxazole formation. The use of an insoluble promoter simplifies the reaction work-up, as only filtration and solvent removal are necessary. Molecular sieve promoted cyclocondensations have proven to be general for a wide variety of reaction partners. Isoxazole products previously prepared by amine-promoted cyclocondensation reactions were easily obtained in essentially identical chemical yields under the milder molecular sieve conditions (Table 2, entries 1, 5 and 6).

In addition, using these reaction conditions, we have realized a broader scope for both the nitrile oxide and diketone reaction partners in the cyclocondensation process. Thus cyclohepta-1,3-dione (entry 2), and 2-hydroxynapthoquinone (entries 8 and 9) were readily employed in the cyclocondensation reaction,[5] affording synthetically useful, highly functionalized products. Stable nitrile oxides **6** and **8** underwent clean cyclocondensation in the presence of MS 4A (entries 3 and 4). Unsymmetrical diketones, such as **15**, also served as viable substrates, giving preferentially one regioisomer (entry 7). Isoxazole products possessing a C-centered stereogenic center (entries 6 and 7) were observed to be diastereomeric mixtures due to hindered rotation about the aryl–isoxazole bond. Preliminary studies, however, suggest that these molecules are not configurationally stable about the biaryl axis.

In conclusion, we have documented the utility of MS 4A as effective reagents for promoting the cyclocondensation of stable, hindered aromatic nitrile oxides with cyclic diketones. The chemical yields, decreased reaction times, and operational simplicity offered by this method enhance its utility for the synthesis of complex heterocycles. The highly functionalized isoxazoles products have found use for the synthesis of benzophenones,[1b] xanthones,[6] stereochemically complex preanthraquinones,[7] and natural products.[8] New methodologies for facile isoxazole synthesis enhance their attractiveness as a platform for the synthesis of complex molecules. The recognition that cyclocondensation reactions can be promoted and accelerated by molecular sieves offers unique mechanistic insights with implications for the further development of highly active and enantioselective catalysts, and of novel carbon–carbon bond forming processes.[9]

A typical experimental procedure is described for the reaction of 2,6-dichlorobenzonitrile oxide (**6**) and cyclohexane-1,3-dione (**2**): To a solution of **6** (56 mg, 0.30 mmol) in 3 mL *i*-PrOH at r.t. was added **2** (41 mg, 0.37 mmol) followed by powdered MS 4A (0.30 g). The yellowish slurry was heated to 50 °C and maintained at this temperature for 15 h. After cooling to r.t., the mixture was filtered, concentrated, and purified by recrystalization (hexane/EtOAc) to afford **7** (67 mg, 80% yield) as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27–2.34 (2 H, m), 2.55 (2 H, dd, *J* = 5.6, 7.6 Hz), 3.13 (2 H, t, *J* = 6.3 Hz), 7.36 (1 H, dd, *J* = 6.5, 9.3 Hz), 7.42 (1 H, d, *J* = 9.3 Hz), 7.42 (1 H, d, *J* = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 23.2, 37.8, 115.4, 126.7, 128.0, 131.3, 135.2, 155.5, 181.3, 191.2. IR (KBr pellet): 3066, 2960, 1688, 1597, 1560, 1460, 1408, 1350, 1197, 1017, 792, 600 cm$^{-1.}$ Anal Calcd for $C_{13}H_9Cl_2NO_2$: C, 55.34; H, 3.22; N, 4.96. Found: C, 55.12; H, 3.25; N, 4.81. Mp 209.6–211.3 °C.

Acknowledgment

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References

(1) (a) Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. *Tetrahedron Lett.* **2003**, *44*, 3555. (b) Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. *Org. Lett.* **2003**, *5*, 391.

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(3) The use of 4 Å MS as a base for the elimination of *C*-chloroximes to form nitrile oxides and subsequent cycloaddition with acrylates has been reported. However, under these conditions long reaction times (7–10 d) were necessary, see: Kim, J. N.; Ryu, E. K. *Heterocycles* **1990**, *31*, 1693.

(4) MS 4A have the general formula $Na_2O·Al_2O_3·xSiO_2·yH_2O$.

(5) Thermal cycloadditions of 2-hydroxynaphthoquinone and nitrile oxides have been previously reported: Brahmeshwari, G.; Rao, V. R.; Rao, T. V. P. *Indian J. Chem., Sect. B* **1995**, *34*, 139.

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(8) Bode, J. W.; Suzuki, K. *Tetrahedron Lett.* **2003**, *44*, 3559.

(9) For a Diels–Alder type cycloaddition reaction promoted by molecular sieves, see: Pindur, U.; Haber, M. *Heterocycles* **1991**, *32*, 1463.