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Aluminium triflate-catalysed regioselective cycloisomerisation of non-activated unsaturated oximes

Xavier Chaminade[a], Shunsuke Chiba[b], Koichi Narasaka[b,*], Elisabet Dunach[a,*]

[a] *Laboratoire de Chimie des Molécules, Bioactives et des Arômes, CNRS, UMR 6001, Institut de Chimie de Nice, Université de Nice-Sophia Antipolis, Parc Valrose, 06108 Nice Cedex 2, France*

[b] *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore*

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Abstract

A novel cycloisomerisation of oximes bearing non-activated C–C double bonds occurs in an Al(III)-catalysed reaction. This process leads to 5-, 6- and 7-membered ring oxygen and nitrogen-containing heterocycles in good yields.

Keywords: Aluminium trifluoromethansulfonate; Cycloisomerisation; Oxime; Oxazepine; Oxazine

Cycloisomerisation of unsaturated hydrocarbons catalysed by transition metal complexes is an efficient and atom economical method for the preparation of various carbocycles and heterocycles.[1] Catalytic cyclisations involving the heteroatom addition to non-activated olefins for the synthesis of heterocyclic compounds have attracted an interest recently. In particular, the intramolecular cyclisation of unsaturated alcohols to cyclic ethers has been recently described using a catalytic amount of Pt(II) in the presence of phosphine ligand.[2] Recent work on Lewis super-acids such as Sn(IV),[3] Al(III)[4] and Cu(II)[5] triflates has also shown high efficiency in cycloisomerisations involving a hydroxyl moiety and non-activated olefins.

We present here our results on the preparation of 1,2-oxaza heterocycles derived from unsaturated oximes by an Al(OTf)$_3$-catalysed cyclisation. Besides the Beckmann rearrangement,[6] the reactivity of oximes and *O*-acyloximes tethered to olefins has been reported to afford intramolecular cyclisations to N-heterocycles (Eq. 1).[7] These reactions involve the formation of intermediate iminyl radicals after the cleavage of the OR moiety, with the further nitrogen addition to the C–C double bond in radical-type processes. Photoinduced radical cyclisation for the synthesis of dihydro-1,2-oxazines has also been reported.[8] Alternatively, the reaction concerning the 1,3-dipolar cycloaddition of oximes with olefins via their rearrangement to nitrones leads to the formation of 1,2-oxazoles.[9–12] The intramolecular cyclisation of oximes with olefins through their oxygen atom has been reported in one case of 1,2-hydroxyiminoketone cyclisation with trifluoroacetic acid,[13] and in one example concerning the cyclisation of allenyloximes for the preparation of oxazepines in the presence of AgBF$_4$.[14]

The reactivity of model oxime **1a** catalysed by different strong Lewis acid metal triflates, used in 20 mol %, was first examined (Eq. 1) and the results are presented in Table 1.[15] Oximes **1** were prepared by reaction of the corresponding ketones with hydroxylamine, and were obtained quantitatively in an approximate 1:1 mixture of (*Z*) and (*E*) isomers. No cyclisation of **1a** occurred with catalysts such as Cu(II), Sn(II), or Fe(III) triflates (entries 1–3), the major reaction product was ketone **3a**, resulting from the hydrolysis of the starting oxime. The hydrolysis of the oxime in

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[*] Corresponding authors. Tel.: +33 0492076142; fax: +33 0492076151 (E.D.).

E-mail addresses: narasaka@ntu.edu.sg (K. Narasaka), dunach@unice.fr (E. Dunach).

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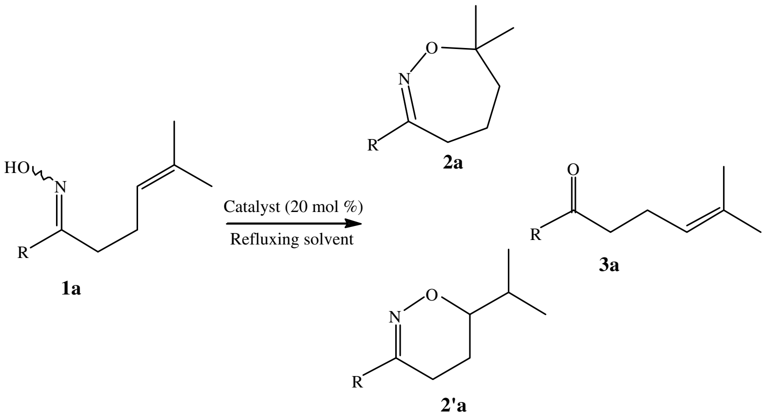


Equation 1. Reaction of 7-methyl-1-phenylo ct-6-en-3-one oxime **1a** catalysed by aluminium(III) triflate.

Table 1
Influence of the catalytic system and of the reaction conditions on the cycloisomerisation of **1a** (catalyst: 20 mol %) in refluxing solvent

Entry	Catalyst/solvent	Reaction time (h)	Conversion (%)	Products, % isolated yield	
				2a	**3a**
1	$Sn(OTf)_2/CH_3NO_2$	24	10	—	10
2	$Fe(OTf)_3/CH_3NO_2$	24	60	—	56
3	$Cu(OTf)_2/CH_3NO_2$	24	95	Traces	86
4	$Al(OTf)_3/CH_3NO_2$	7	92	84	7
5	$Al(OTf)_3/(CH_2Cl)_2$	24	73	59	14
6	$Al(OTf)_3/CH_2Cl_2$	24	10	—	10
7	$TfOH/CH_3NO_2$	24	22	—	22

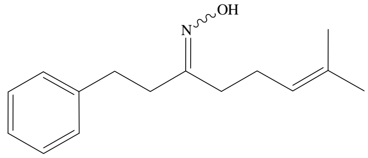
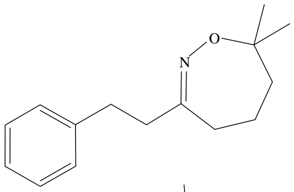
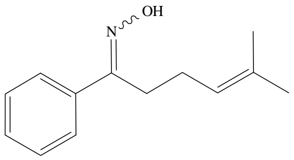
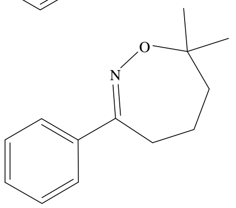
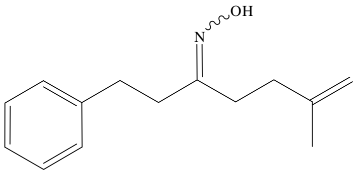
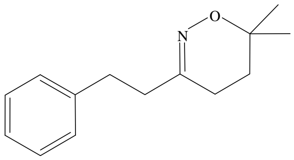
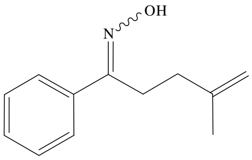
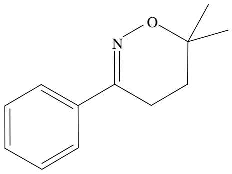
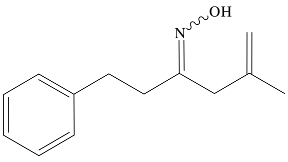
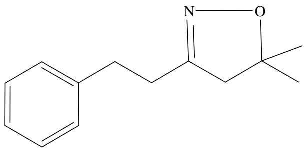
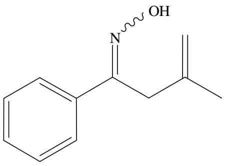
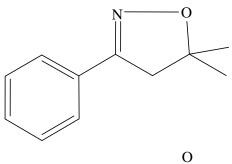
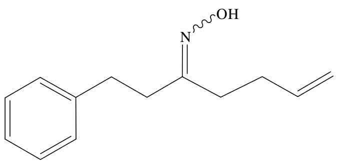
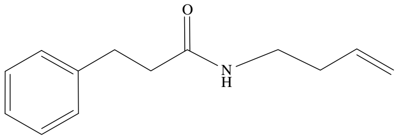
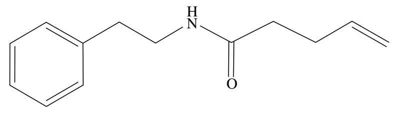
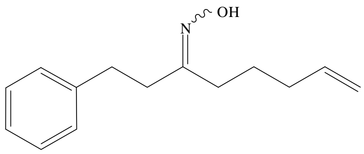
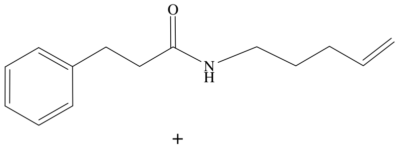
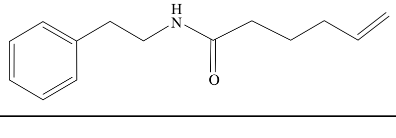
the reaction medium can be explained by the water content of the triflate catalyst. However, the desired intramolecular cyclisation of **1a** occurred in good yield when aluminium(III) triflate was used as the catalyst in refluxing nitromethane (entry 4). With this catalytic system, the cyclisation reaction was very selective; no isomeric 6-membered ring **2′a** was formed and interestingly no amides issued from a Beckmann rearrangement and no products from a 1,3-dipolar cycloaddition of nitrones were obtained. The formation of 1,2-oxazepane **2a** results from the regioselective intramolecular addition of the hydroxyl group of **1a** on the most substituted carbon of the C–C double bond. It is noteworthy that a 7-membered ring heterocycle was formed selectively in high yield in this Lewis acid-catalysed cycloisomerisation reaction.

The influence of the temperature and solvent was examined with **1a** and $Al(OTf)_3$ (entries 4–6). The cycloisomerisation of **1a** occurred efficiently in refluxing dichloroethane, yielding **2a** in 59%; the reaction was faster in refluxing nitromethane and led to an isolated yield of 84% after 7 h (entries 4 and 5). Product decomposition was observed at higher temperatures, for example, in refluxing xylene.

When oxime **1a** was reacted with triflic acid (CF_3SO_3H, entry 7) with the same catalyst ratio, a conversion of 22% was reached after 24 h in refluxing nitromethane, leading to the exclusive formation of ketone **3a**. In other metal triflate-catalysed processes, it has been suggested that the active catalyst was TfOH;[16] however, in the present cycloisomerisation, the strong difference of reactivity using $Al(OTf)_3$ and TfOH as catalysts (compare entries 4 and 7) is worth noting and highlights the efficiency of $Al(OTf)_3$ in the catalytic process.

The reaction was then extended to several oximes **1b**–**h** bearing different mono-, di- and trisubstituted double bonds and the results are presented in Table 2. In the case of oximes bearing trisubstituted double bonds such as **1a** and **1b** (entries 1 and 2), the reaction occurred smoothly in refluxing nitromethane and afforded the 7-membered ring structures **2a** and **2b**, in 84% and 80% isolated yields, respectively. In refluxing dichloroethane, the reaction rates were diminished. A new C–O bond was regioselectively formed between the oxime oxygen and the most substituted end of the olefin, following a Markovnikov-type addition on the double bond. When the oxime was tethered to a terminal disubstituted double bond such as in substrates **1c**–**f**, the reaction led to the formation of the corresponding 5- or 6-membered rings (entries 3–6). Thus, six membered ring N,O-heterocycles were isolated from **1c** and **1d** (entries 3 and 4) in 82% and 81% yields, respectively. For substrates **1e** and **1f**, 1,2-oxazolines **2e** and **2f** were obtained in 73% and 84% yields, respectively (entries 5 and 6). 1,2-Oxazolines, 1,2-oxazines or 1,2-oxazepines were obtained depending on the double bond substitution and the chain length between the oxime moiety and the double bond. Oximes bearing terminal monosubstituted double bonds such as **1g** and **1h** presented a different reactivity, affording amides **4** and **5**, respectively, through a Beckmann rearrangement.[6] Isomeric amides **4**/**5** were

Table 2
Reaction of non-activated unsaturated oximes **1a**–**h** catalysed by Al(OTf)$_3$ (20 mol %)[15]

Entry	Substrate	Solvent (reflux)/ reaction time (h)	Product	Isolated yield (%)	Regioselectivity (**2**:**2′**)
1	**1a** 	MeNO$_2$/12	 **2a**	84	>98:—
2	**1b** 	MeNO$_2$/12	 **2b**	80	>98:—
3	**1c** 	(CH$_2$Cl)$_2$/12	 **2c**	82	>98:—
4	**1d** 	(CH$_2$Cl)$_2$/12	 **2d**	81	>98:—
5	**1e** 	(CH$_2$Cl)$_2$/12	 **2e**	73	>98:—
6	**1f** 	(CH$_2$Cl)$_2$/12	 **2f**	84	>98:—
7	**1g** 	MeNO$_2$/12	 **4g** +  **5g**	82	**4g**:**5g** ≈ 1:1
8	**1h** 	MeNO$_2$/12	 **4h** +  **5h**	74	**4h**:**5h** ≈ 1:1

obtained in 74–82% yields as approximately 1:1 mixtures (entries 7 and 8).

To explain the cyclisation regioselectivity, an electrophilic attack of the oxime proton on the double bond, after its activation by complexation to the highly electrophilic Al^{3+}, can be proposed. The acidity of the oxime proton should be strongly enhanced by $Al(OTf)_3$, as in the case of the cyclisation of unsaturated alcohols.[4]

In conclusion, this work presents the use of aluminium(III) triflate as an efficient catalyst in the cycloisomerisation of non-activated olefinic oximes. The reaction is completely regiospecific and allows the formation of differently substituted cyclic 1,2-oxaza derivatives such as oxazepines, oxazines and oxazolines in good yields with oximes bearing di- and trisubstituted double bonds. The cyclisation follows a Markovnikov-type addition of the oxime–O–H group on the double bond.

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14. Grimaldi, J.; Cormons, A. *Tetrahedron Lett.* **1985**, *26*, 825–828.
15. Procedure for cycloisomerisation of oximes, **1**: $Al(OTf)_3$ (0.2 mmol) was added under nitrogen to freshly distilled solvent (5 mL) and the solution heated to reflux. The oxime (1 mmol, neat) was introduced and the solution stirred for the reported time. After complete consumption (or negligible evolution, GC analysis), the reaction mixture was quenched with aqueous 0.1 M HCl solution and extracted with Et_2O. The organic layers were dried over $MgSO_4$, concentrated under vacuum and purified by column chromatography on silica-gel, using hexane/Et_2O mixtures (95:5 to 80:20) as eluents. Compounds **2** were obtained as colourless liquids and were characterised by ^1H and ^{13}C NMR and by mass spectrometry. Spectral data for **2a**, 7,7-dimethyl-3-(2-phenylethyl)-4,5,6,7-tetrahydro-1,2-oxazepine, as a representative example: ^1H NMR (500 MHz): δ 7.27–7.07 (m, 5H), 2.96 (dd, $^3J = 7.2$, $^3J = 7.7$ Hz, 2H), 2.74 (dd, $^3J = 7.2$, $^3J = 7.7$ Hz, 2H), 2.41 (t, $^3J = 6.4$ Hz, 2H), 1.87–1.78 (m, 2H), 1.66–1.55 (m, 2H), 1.49 (s, 6H). ^{13}C NMR (125 MHz): δ 158.73, 141.06, 128.90, 128.74, 126.52, 66.12, 37.47, 35.06, 31.30, 30.45, 27.49, 16.02. MS (70 eV): 231 (M^+, 46), 216 (29), 110 (38), 91 (100), 77 (13), 65 (19), 55 (18).
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