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Microwave-assisted highly diastereoselective synthesis of oxazolidines derived from ketones and aminoalcohols

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ABSTRACT

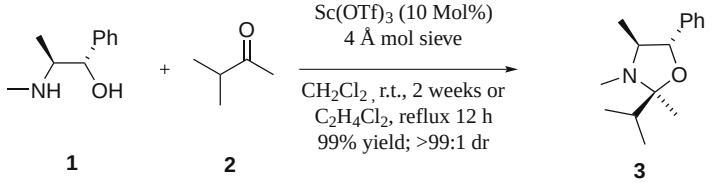
A number of oxazolidines derived from ketones and aminoalcohols have been prepared in excellent yields using microwave irradiation. In most cases, conventional reflux failed to provide any of the desired products.

1. Introduction

The synthesis of oxazolidines derived from aminoalcohols and aldehydes is well documented, but oxazolidines derived from ketones have only been reported infrequently, presumably as a result of the slow rate at which they are formed.[1] They are also easily hydrolysed as a result of the additional stabilization of the incipient iminium ion in the ring-opened tautomer. Recent interest in the use of oxazolidines as ligands and as organocatalysts,[2] coupled with several ongoing projects in our laboratories, has prompted us to investigate the synthesis of oxazolidines derived from ketones and aminoalcohols.[3]

We have recently reported the use of scandium triflate in the presence of carefully dried 4 Å molecular sieve to mediate oxazolidine synthesis from aminoalcohols and ketones. Reactions were carried out initially in dichloromethane (DCM) at room temperature or reflux, and later in 1,2-dichloroethane (DCE) at reflux, and were monitored by ^{1}H and ^{13}C NMR spectroscopy; the ^{13}C NMR chemical shift at position 2 in the oxazolidine products is observed at δ_C 96–99 ppm and is diagnostic. For example, when pseudoephedrine **1** was treated with isopropyl methyl ketone **2** (1.0 equiv), scandium triflate (10 mol %) and molecular sieve, the oxazolidine **3** was formed in almost quantitative yield, and only one diastereoisomer could be detected by ^{1}H NMR spectroscopy (Scheme 1); the stereochemistry was determined by NOE analysis. The reactions were very clean; products were isolated after stirring the reaction mixtures with anhydrous sodium hydrogen carbonate in order to remove adventitious protic acid and the Lewis acid.

The use of microwave-assisted reactions has, over the past decade, increased dramatically, and we have exploited this technology for Mannich reactions involving tetraalkoxyresorcin[4]arenes.[4] Experiments were carried out using a CEM Discover focused microwave apparatus; we observed that reactions could be carried out with much reduced reaction times and that improved yields and cleaner products could be obtained. Following this work and noting the long reaction times required for oxazolidine formation (ca. 1–14 days),[3] we decided to investigate the formation of oxazolidines from ketones using microwave irradiation.



1 2 3

Scheme 1.

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E-mail address: p.page@uea.ac.uk (P. C. Bulman Page).

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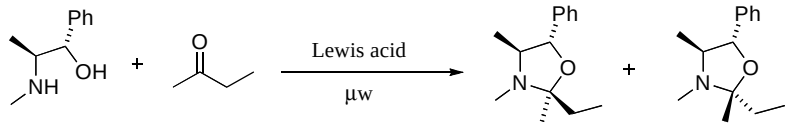
Table 1
Screening of various acids for the synthesis of oxazolidines **5** and **6**[a]

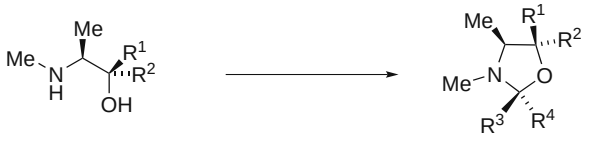


1 **4** **5** **6**

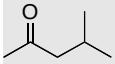
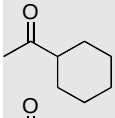
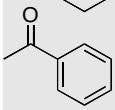
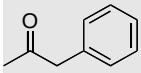
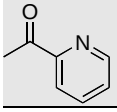
Acid	Temperature[b] (°C)	Solvent	Time	d.r. [**5**:**6**][c]	Yield (%)
$Sc(OTf)_3$	83 (reflux)[d]	DCE	12 h	5.7:1	88
—	100	Neat	2 × 5 min	—	<5
$Sc(OTf)_3$	100	Neat	2 × 5 min	—	<5
$Sc(OTf)_3$	100	DCE	2 × 5 min	4:1	51
$Sc(OTf)_3$	100	Neat	2 × 10 min	4:1	54
$Sc(OTf)_3$	100	Neat	30 min	—	Dec.
$Sc(OTf)_3$	120	Neat	5 min	—	Dec.
$BF_3{\cdot}Et_2O$	100	Neat	5 min	4:1	91[e]
$BF_3{\cdot}Et_2O$	100	Neat	5 min	4:1	86[e,f]
$TiCl_4$	100	Neat	5 min	3.1:1	20
p-TsOH	100	Neat	5 min	3.4:1	75
CSA	100	Neat	5 min	3.3:1	89

[a] Reaction conditions: pseudoephedrine (1.0 mmol), butan-2-one (1.5 mmol), acid (10 mol %), CEM discover microwave set at a maximum of 300 W with cooling activated.
[b] Microwave instrument temperature indication except for conventional reflux experiments.
[c] Major diastereoisomer determined by NOE analysis.
[d] Conventional reflux in solution.
[e] Average yield of two runs.
[f] Reaction carried out on a 12 mmol scale.

Table 2
The synthesis of several oxazolidines from ephedrine and pseudoephedrine[a]



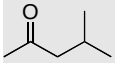
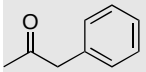
(1*S*,2*R*)-Ephedrine: R^1= Ph, R^2 = H
(1*S*,2*S*)-Pseudoephedrine : R^1= H, R^2 = Ph

Ketone	β-Aminoalcohol	Lewis acid	Conditions, temperature[b] (°C)	Solvent	Reaction time	d.r.	Yield (%)
	Ephedrine	$Sc(OTf)_3$	Reflux, 83	DCE	12 h	2:1	94
		$Sc(OTf)_3$	Microwave, 100	Neat	2 × 5 min	2:1	52
		$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	2:1	38
		$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	2 × 5 min	2:1	78
	Pseudo-ephedrine	$Sc(OTf)_3$	Reflux, 83	DCE	12 h	5.7:1	88
		$Sc(OTf)_3$	Microwave, 100	Neat	2 × 5 min	4:1	51
		$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	4:1	91
	Ephedrine	$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	2 × 5 min	2:1	67
	Pseudo-ephedrine	$Sc(OTf)_3$	Microwave, 100	Neat	2 × 5 min	9:1	65
		$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	9:1	88
	Ephedrine	$Sc(OTf)_3$	Reflux, 83	DCE	7 d	97:1	95
		$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	5.6:1	26
		$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	10 min	5.6:1	30
	Pseudo-ephedrine	$Sc(OTf)_3$	Reflux, 83	DCE	2 d	97.5:1	96
		$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	97.5:1	95
	Ephedrine	$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	2 × 5 min	6:1	54
	Pseudo-Ephedrine	$Sc(OTf)_3$	Reflux, 83	DCE	2 d	97.5:1	88
		$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	97.5:1	87
	Ephedrine	$Sc(OTf)_3$	Reflux, 83	DCE	14 d	—	NR
		$BF_3{\cdot}Et_2O$	Microwave, 80	Neat	10 min	—	NR
	Pseudo-ephedrine	$Sc(OTf)_3$	Reflux, 83	DCE	7 d	97.5:1	55
		$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	5.7:1	90
	Ephedrine	$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	2 × 5 min	3:2	77
	Pseudo-Ephedrine	$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	6:1	78
	Ephedrine	$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	2 × 5 min	1.3:1	85
	Pseudo-ephedrine	$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	3.7:1	93

[a] Reaction conditions: aminoalcohol (1.0 mmol), ketone (1.5 mmol), acid (10 mol %), CEM Discover Microwave set at a maximum of 300 W with cooling activated.
[b] Microwave instrument temperature indication except for conventional reflux experiments.

Table 3
The synthesis of several oxazolidines from 1,2,3,4-tetrahydroisoquinolin-3-yl methanol **7**[a]

7

Ketone	Lewis acid	Conditions, temperature[b] (°C)	Solvent	Reaction time	d.r.	Yield (%)
	$Sc(OTf)_3$	Reflux, 83	DCE	12 h	1.5:1	42
	$Sc(OTf)_3$	Microwave, 100	Neat	2 × 5 min	1.5:1	40
	$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	1.5:1	53
	$Sc(OTf)_3$	Microwave, 100	Neat	2 × 5 min	4:1	51
	$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	4:1	58
	$Sc(OTf)_3$	Reflux	DCE,	3 d	11:1	43
	$Sc(OTf)_3$	Reflux	DCE,	7 d	—	Dec.
	$Sc(OTf)_3$	Microwave, 120	Neat	10 min	11:1	57
	$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	11:1	25
	$BF_3{\cdot}Et_2O$	Microwave, 100 + 4 Å mol sieves	Neat	5 min	11:1	50
	$Sc(OTf)_3$	Reflux	DCE,	3 d	20:1	33
	$Sc(OTf)_3$	Microwave, 100	Neat	10 min	20:1	38
	$BF_3{\cdot}Et_2O$	Microwave, 100	Neat	5 min	20:1	40

[a] Reaction conditions: 1,2,3,4-tetrahydroisoquinolin-3-yl methanol **7**, (1.0 mmol), ketone (1.5 mmol), acid (10 mol %), CEM Discover Microwave set at a maximum of 300 W with cooling activated.
[b] Microwave instrument temperature indication except for conventional reflux experiments.

We initially ran a range of reactions using scandium triflate, as this Lewis acid had shown the best reaction profile, in terms of yield and diastereoselectivity, for our previously published process using classical reflux conditions.[3] We were, however, unable to attain the level of yield or diastereoselectivity obtained when using the scandium triflate/dichloroethane/reflux conditions. We therefore screened a range of Lewis and protic acids with the most reactive aminoalcohol and ketone (pseudoephedrine and butan-2-one **4**) (Table 1).

We observed that in the absence of acid no oxazolidine was formed; on addition of $Sc(OTf)_3$, however, we saw a much reduced reaction time, although we were unable to increase the yield from 54% without decomposition products being formed. A range of other acids were tested, and $BF_3{\cdot}Et_2O$ appears to be the catalyst of choice, affording 91% of the desired oxazolidines **5** and **6** in just 5 min. This is remarkable when considering that reaction times for the corresponding reaction under classical reflux conditions were at least 12 h. We were also able to conduct the reaction on a larger scale (12 mmol) and were delighted to observe similar high yields. Having established the optimum conditions, we conducted several further reactions to produce a range of oxazolidines from various ketones and ephedrine or pseudoephedrine (Table 2).

Following our success in the synthesis of oxazolidines from pseudoephedrine and ephedrine, we next turned our attention to the synthesis of oxazolidines derived from 1,2,3,4-tetrahydroisoquinolin-3-yl methanol **7**, as these products would provide valuable intermediates for other projects within our laboratories (Table 3).

Formation of the oxazolidines from **7** proved more problematic than from ephedrine or pseudoephedrine. In each case the yield was slightly improved when using the microwave reactor, but any further attempts to optimize the system beyond 60% yield proved unsuccessful. One possible explanation for this arises from the relative lack of stability of the oxazolidine products.

In summary, we have developed a useful procedure for the rapid formation of oxazolidines derived from ketones and aminoalcohols, with reaction times being dramatically reduced when compared to traditional heating conditions (1–14 days reduced to 10 min). In each case the yield of the reaction was also increased when using microwave irradiation.

2. Typical experimental procedure

2.1. (+)-(2*S*,4*S*,5*S*)-2-Isopropyl-5-phenyl-2,3,4-trimethyloxazolidine

Pseudoephedrine (0.50 g, 3.0 mmol) and 3-methylbutanone (0.26 g, 3.0 mmol) were added to a CEM Discover microwave reaction tube containing a Teflon stirrer bar. The vial was capped, purged with N_2 and $BF_3{\cdot}Et_2O$ (0.4 mL, 0.3 mmol) was added dropwise. The reaction mixture was transferred to the microwave and irradiated at a fixed temperature of 100 °C for 5 min with cooling activated. The mixture was diluted with dichloromethane (5.0 mL) and copper sulfate solution (1.0 mL, 5%), and stirred for 10 min at room temperature. The aqueous phase was extracted with dichloromethane (10 mL), and the combined organic layers washed with saturated aqueous Rochelle salt (5.0 mL) and dried ($MgSO_4$). The solvents were removed under reduced pressure to afford the product as a colourless oil (0.67 g, 95%). $[\alpha]_D$ +39.0 (*c* 1.00, CCl_4); ν_{max} (neat)/cm^{-1} 3130, 2924, 2761, 1459, 1373, 1326, 1189, 1135; δ_H (250 MHz; $CDCl_3$) 0.95 (3H, d, *J* 2.8 Hz), 0.98 (3H, d, *J* 2.8 Hz), 1.01 (3H, d, *J* 6.0 Hz), 1.25 (3H, s), 1.70–1.86 (1H, m), 2.20 (3H, s) 2.41–2.50 (1H, m), 4.30 (1H, d, *J* 8.9 Hz), 7.22–7.40 (5H, m); δ_C (100 MHz; $CDCl_3$) 7.7, 14.4, 14.6, 33.7, 36.4, 65.1, 85.4, 98.6, 126.2, 126.7, 127.0, 127.7, 140.4; *m/z* 234.1801; $C_{15}H_{24}NO$ (M^++H) requires 234.1799.

Acknowledgements

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References and notes

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