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Microwave promoted oxazole synthesis: cyclocondensation cascade of oximes and acyl chlorides

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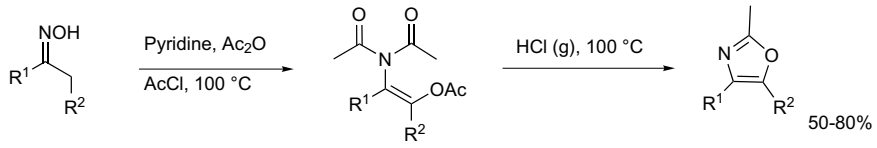
Abstract—Microwave irradiation promotes the rapid *O*,*N*-acylation–cyclodehydration cascade reaction of oximes and acid chlorides to give oxazoles.

Oxazoles are key building blocks of natural products, pharmaceuticals, and synthetic intermediates.[1] They are most commonly obtained by the Hantzsch reaction[2] or the cyclodehydration of β-ketoamides.[3] The dehydrogenation of oxazolines[4] and other processes such as aza-Wittig reactions,[5] Schmidt rearrangements,[6] the use of isocyanides,[7] TosMIC,[8] and intramolecular alkyne additions[9] have also been employed. An interesting conversion of ketoximes to oximes via *N*,*N*-diacylated enamides was reported in 1980 by Bhat and Reddy (Scheme 1).[10] While, quite likely due to the harsh thermal and acidic conditions and long reaction times this reaction was rarely applied,[11] we were intrigued by the possibility to optimize this procedure and generate conditions for a streamlined process in the microwave reactor.

Microwave chemistry is becoming increasingly popular;[12] however, there are few examples of oxazole formations using microwave irradiation. Lee et al. developed a solvent free method in which [hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo]benzene (HDNIB) reacts with various ketones in a household microwave to form α-[(2,4-dinitrobenzene)sulfonyl]oxy ketones, which are converted to oxazoles through treatment with amides.[13a] Similarly, reacting ketones with benzonitrile and mercury(II) *p*-toluenesulfonate yielded substituted oxazoles in the microwave.[13b] Our first attempts of employing Malamas et al.'s conditions[11] for converting oxime **1** to oxazole **3** with acid chloride **2** under microwave irradiation at various temperatures in pyridine/toluene (5.6:1) did not lead to oxazole formation (Scheme 2, Table 1). We switched to 1,2-dichlorobenzene, a more polar solvent that was better suited for microwave irradiation, and catalytic DMAP was added in an attempt to facilitate acyl transfer processes. Several temperatures and various reaction times were explored until we obtained moderate isolated yields of oxazole. Both thermal and microwave reactions failed with anhydrides or acyl imidazoles, but under optimized microwave conditions, a range of oximes and acyl chlorides were converted to the desired heterocycles (Scheme 3, Table 2).[14] While the yields were variable, the scope of oxime substituents was quite broad, and both cyclic



Scheme 1. Oxazole synthesis from ketoximes and acetyl chloride under conventional conditions.[10]

Keywords: Microwave; Oximes; Oxazoles; Cascade reaction; Rearrangement.
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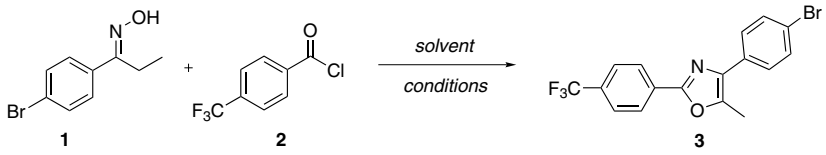
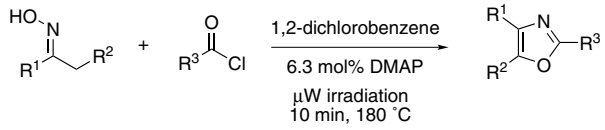


Scheme 2. Cyclocondensation of oxime **1** and acyl chloride **2** leading to oxazole **3**.

Table 1. Reaction optimization for microwave promoted oxazole formation

Entry	Solvent (v/v)	Conditions	Additive	**3** (Yield/%)[b]
1	Pyridine/toluene (5.6:1)	100 °C, 24 h	—	—
2	Pyridine/toluene (5.6:1)	μW, 180 °C, 10 min	—	—
3	1,2-Dichlorobenzene	μW, 115 °C, 30 min	DMAP[a]	—
4	1,2-Dichlorobenzene	μW, 160 °C, 45 min	DMAP[a]	16
5	1,2-Dichlorobenzene	μW, 180 °C, 10 min	DMAP[a]	34
6	1,2-Dichlorobenzene	μW, 220 °C, 5 min	DMAP[a]	Trace

[a] 6.3 mol % of DMAP was used.
[b] Isolated yields after chromatography on SiO_2.Yields are based on oximes.



Scheme 3. Oxazole formation under microwave irradiation (μW) conditions.

and acyclic, aromatic and aliphatic ketoximes work well. Some of the starting material was recovered, but most of the remaining mass balance was converted into intractable polar side products. Interestingly, we found that the yield was higher for the more readily enolizable oximes. This is particularly well illustrated in entries 7 and 8 in Table 2. In addition, we found that methyl aryl ketone derived oximes did not provide oxazoles under either thermal or microwave conditions. In the presence of carboxyl groups with enolizable α-positions, oxazole formation also failed for reasons that are not yet clear.

In addition to a much faster conversion, the major advantage of microwave irradiation was a considerably increased yield. Control reactions with oxime **13** and acid chloride **2** under a range of thermal and optimized microwave conditions shown in Table 3 illustrate the improvement in the reaction process using microwave technology.

In conclusion, we have investigated the scope of the preparation of substituted oxazoles from oximes and acid chlorides and improved this methodology by using a monomode microwave generator. The microwave irradiation allowed considerable acceleration of the rate of oxazole formation and increased the yield of this synthetically attractive heterocycle formation process. The starting oximes were readily obtained from commer-

Table 2. Oxazole preparations under optimized microwave irradiation conditions[15]

Entry	R_1	R_2	Oxime	R_3	Oxazole	Yield (%)[a]
1	*p*-BrC_6H_4	Me	**1**	*p*-$CF_3C_6H_4$	**3**	34
2	*p*-BrC_6H_4	Me	**1**	Ph	**4**	26
3	*p*-BrC_6H_4	Me	**1**	*t*-Butyl	**5**	26
4	Et	Me	**6**	*p*-$CF_3C_6H_4$	**7**	53
5	Et	Me	**6**	*p*-$CH_3OC_6H_4$	**8**	38
6	*i*-Propyl	Me	**9**	*p*-$CF_3C_6H_4$	**10**	53
7	Ph	Me	**11**	*p*-$CF_3C_6H_4$	**12**	23
8	Me	Ph	**13**	*p*-$CF_3C_6H_4$	**14**	62
9			**15**	*p*-$CF_3C_6H_4$	**16**	38
10			**15**	$BnOCH_2$	**17**	28
11			**15**	$C_6H_5CH{=}CH$	**18**	25
12			**19**	*p*-$CF_3C_6H_4$	**20**	40

[a] Isolated yields after chromatography on SiO_2. Yields are based on oximes.

Table 3. Comparison of thermal and microwave conditions for the conversion of oxime **13** and acid chloride **2** to oxazole **14**

Entry	Solvents	Time	Temperature	**14** (Yield/%)[a]
1	Toluene/pyridine, 5.6:1 (v/v)	24 h	100 °C	30
2	Toluene/pyridine, 5.6:1 (v/v)	12 h	120 °C	34
3	1,2-Dichlorobenzene	10 min	180 °C[b]	43
4	1,2-Dichlorobenzene	10 min	180 °C (μW)	62

Entries 1–3 are under standard thermal conditions.
[a] Isolated yields after chromatography on SiO_2. Yields are based on oximes.
[b] A sand bath was preheated to 180 °C.

cially available ketones in yields exceeding 90%, and the yields of isolated oxazoles ranged from 23% to 62%.

Acknowledgments

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15. In a typical procedure, oxime (1.0 equiv) and acid chloride (2.5 equiv) were added to 1,2-dichlorobenzene to give a 2.5 M solution. After addition of 6.3 mol % of DMAP, the reaction mixture was heated in the microwave for 10 min at 180 °C (150 W), poured into water, extracted with ethyl acetate, dried ($MgSO_4$), and concentrated. The residue was purified using chromatography on SiO_2 to afford the pure oxazole. 4-Ethyl-5-methyl-2-(4-trifluoromethylphenyl)-oxazole (**7**). To a solution of 3-pentanone oxime **6** (37.4 mg, 0.370 mmol) and DMAP (2.40 mg, 0.0196 mmol) in 1,2-dichlorobenzene (0.140 mL) at 0 °C was added dropwise 4-trifluoromethylbenzoyl chloride (140.0 μL, 0.915 mmol). The reaction mixture was heated in the microwave for 10 min at 180 °C (150 W) and poured into water (5 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 20:1) to give (50.0 mg, 53%) of **7** as a colorless solid: mp 57.0–58.8 °C (hexanes/EtOAc); IR (neat) 2965, 2931, 1617, 1414, 1329, 1322, 1298 cm^{-1}; ^1H NMR 8.10 (d, 2H, J = 8.2 Hz), 7.68 (d, 2H, J = 8.3 Hz), 2.54 (q, 2H, J = 7.6 Hz), 2.36 (s, 3H), 1.26 (t, 3H, J = 7.5 Hz); ^{13}C NMR 157.8, 143.8, 138.3, 131.1 (q, J = 32.3 Hz), 131.0, 126.0, 125.7, 124.0 (q, J = 270.7 Hz), 19.2, 13.7, 10.2; MS (EI) *m/z* (rel intensity) 255 (M^+, 100), 240 (96), 173 (21), 172 (42), 145 (17); HRMS (EI) *m/z* calcd for $C_{13}H_{12}F_3NO$ 255.0871, found 255.0874. 2-Styryl-4,5,6,7-tetrahydrobenzoxazole (**18**). To a solution of cyclohexanone oxime **15** (28.0 mg, 0.250 mmol) and DMAP (2.00 mg, 0.0163 mmol) in 1,2-dichlorobenzene (0.100 mL) at 0 °C was added cinnamoyl chloride (105.0 mg, 0.630 mmol). The reaction mixture was heated in the microwave for 10 min at 180 °C (150 W) and poured

into water (5 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to give (14.0 mg, 25%) of **18** as a yellow solid: mp 113–115 °C (hexanes/EtOAc); IR (neat) 2927, 2846, 1701, 1639, 1546, 1525, 1493, 1444 cm^{-1}; ^1H NMR δ 7.55–7.47 (m, 3H), 7.42–7.28 (m, 3H), 6.89 (d, 1 H, J = 16.4 Hz), 2.73–2.63 (m, 2H), 2.62–2.52 (m, 2H), 1.98–1.79 (m, 4H); ^{13}C NMR δ 159.8, 146.8, 136.1, 135.5, 134.4, 128.9, 128.8, 127.1, 114.5, 23.2, 23.1, 23.0, 22.1; MS (EI) *m*/*z* (rel intensity) 225 (M^+, 62), 224 ($[M-H]^+$, 100), 196 (25), 168 (9), 115 (61); HRMS (EI) *m*/*z* calcd for $C_{15}H_{14}NO$ 224.1075 (M−H), found 224.1075.