Rapid Synthesis of Oxazoles under Microwave Conditions

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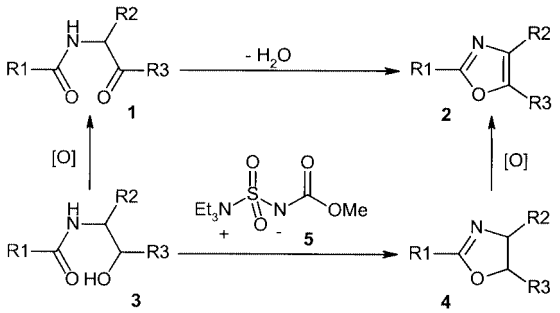
Abstract: A new and efficient variation of the Robinson-Gabriel oxazole synthesis is described. Oxazoles were prepared by cyclodehydration of 2-acylamino carbonyl compounds with Burgess reagent under monomode microwave irradiation.

Key words: oxazoles, cyclization, microwaves

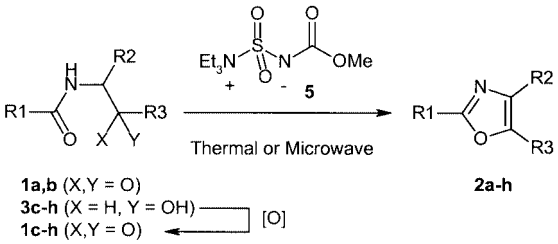
The cyclodehydration of 2-acylamino ketones (**1**, R3 ≠ H), known as the Robinson-Gabriel reaction,[1] is one of the oldest and most widely used syntheses of 2,5-disubstituted and 2,4,5-trisubstituted oxazoles **2**, Scheme 1. Classically, this transformation is carried out with relatively harsh dehydrating agents including concentrated H_2SO_4, polyphosphoric acid, P_2O_5, $SOCl_2$, $POCl_3$ and anhydrous HF.[2] Recent synthetic efforts towards oxazole-containing natural products have prompted interest in milder dehydration conditions, which offer broader functional group compatibility.[3] 2-Monosubstituted and 2,4-disubstituted oxazoles are generally inaccessible by the Robinson-Gabriel method owing to the sensitivity of 2-acylamino aldehydes (**1**, R3 = H) to oxidative and dehydrating conditions.[4] As a partial solution to these limitations oxazoles may be synthesized by mild cyclodehydration of 2-acylamino alcohols **3** with Burgess reagent **5**[5,6] followed by oxidative aromatization of the oxazolines **4**. This approach is restricted by the lack of efficient, general methods for the oxidation step[7] but is useful for the synthesis of 4-carboxyoxazoles.[8] To date, there are no reports of the use of Burgess reagent to *directly* effect the cyclodehydration of 2-acylamino carbonyl compounds **1**.



Scheme 1

We provide herein a preliminary account of a novel variation of the Robinson-Gabriel reaction, which utilizes Burgess reagent **5** as a mild dehydrating agent under monomode microwave conditions.

A selection of 2-acylamino carbonyl compounds **1a-h** (Scheme 2 and Table 1) was prepared. **1a,b** were synthesized by acylation of 2-aminoacetophenone hydrochloride with acetic or benzoic anhydride.[9] **1c-h** were synthesized by oxidation of the 2-acylamino alcohols **3c-h** using either catalytic TPAP/NMO[10] or catalytic TEMPO/sodium hypochlorite in a biphasic system.[11,12] These reactions were not optimized.



Scheme 2

Initially, the compounds **1a-h** (20 mg) were treated with Burgess reagent **5** (2.0 eq.) in THF (1 ml) at reflux for 2 h. The reactions were conducted in parallel and care was taken to use Burgess reagent from a single batch.[13] Following a methanol quench, LC-MS showed in each case clean conversion to the oxazole. However, the apparent reaction rates varied considerably (Table 1). In particular, cyclodehydration of **1b,d** and the valylthreonine derivative **1f** were sluggish. Decomposition of the 2-acylamino aldehydes **1g,h** under LC conditions prevented an accurate measure of their conversion to oxazoles **2g,h** but in both cases the major LC peak after 2 h reaction time corresponded to the oxazole.

The use of flash-heating by microwave irradiation to promote the rate of reactions has received considerable attention of late.[14] We recently reported the cyclodehydration of 1,2-diacylhydrazines to 1,3,4-oxadiazoles using Burgess reagent under microwave irradiation.[15] In an attempt to increase the rate of cyclodehydration of the 2-acylamino carbonyl compounds **1a-h**, the above reactions were repeated under microwave conditions: the reactions were carried out in a sealed vessel under monomode microwave irradiation (continuous irradiation at 2450 MHz) in a Labwell Microwell 10 apparatus. Generally, complete conversion of the 2-acylamino carbonyl compounds **1a-h** to the oxazoles **2a-h** was achieved within several minutes. In some cases it was necessary to apply two cycles of microwave irradiation and to add additional Burgess reagent be-

Table 1 Data for the Synthesis of Oxazoles **2**

	R1	R2	R3	Yield of **1** (%)[a]	Thermal **1:2** (LC-MS)[b]	Microwave Conditions		
						Irradiation Time/Power	Eqs **5**	Yield of **2** (%)[a]
a	Me	H	Ph	78[c]	32:68	2 min @ 100 W	1.5	80
a	Me	H	Ph			2 min @ 100 W	1.5[d]	72
b	Ph	H	Ph	84[c]	77:23	2 x 10 min @ 50 W	1 + 1	93
c	Ph	H	Me	56[e]	10:90	2 min @ 100 W	1	100
c	Ph	H	Me			2 min @ 100 W	1.8[d]	91
d[f]	Me	Me	Ph	100[e]	78:22	2 x 4 min @ 100W	1 + 1	83
e[f]	Ph	Me	Ph	100[g]	3:97	4 min @ 100 W, 2 min @ 200 W	1 + 1	82
f	(*S*)-ZHNCH(i-Pr)	CO_2Me	Me	53[g]	56:44	2 min @ 150 W, 2 min @ 180 W	2 + 2	95
g	3-Phenoxyphenyl	H	H	85[h]	-[i]	1 min @ 100 W	1	93
g	3-Phenoxyphenyl	H	H			1 min @ 100 W	1.1[d]	79
h	2,4-Dimethylphenyl	H	H	90[h]	-[i]	2 x 1 min @ 100 W	1 + 0.5	81

[a]Yields refer to isolated products. [b]**5** (2.0 eqs), THF, reflux, 2 h. [c]Prepared from 2-aminoacetophenone.HCl. [d]PEG-supported Burgess reagent was used. [e]TPAP (5 mol%), NMO, 4 Å molecular sieves, DCM. [f]Derived from (1*R*,2*S*)-norephedrine. [g]TEMPO (5 mol%), $NaHCO_3$, NaOCl, DCM, H_2O. [h]TEMPO (5 mol%), $NaHCO_3$, NaOCl, EtOAc, H_2O. [i]**2g,h** were unstable to LC conditions.

tween the cycles. When TLC and LC-MS analysis indicated the absence of starting material, the crude reaction mixtures were passed through a short column of silica gel to remove the polar degradation products of Burgess reagent. Examples of 2-, 2,5- and 2,4,5-substituted oxazoles were synthesized. This procedure is very convenient to carry out, avoids tedious work up and purification, and rapidly provides high yields of oxazoles.[16,17] Polyethylene glycol-supported Burgess reagent[13,15] was also used successfully in several cases, however, a moderate reduction in yield was observed. Details of the microwave conditions and yields are reported in Table 1.

The high yielding synthesis of the 2-monosubstituted oxazoles **1g,h** from the parent 2-acylamino alcohols **3g,h** by catalytic TEMPO oxidation followed by cyclodehydration with Burgess reagent is particularly noteworthy. This represents a synthetically useful extension of the scope of the Robinson-Gabriel process to include the hitherto problematic 2-acylamino aldehydes.[4]

In summary, we have devised an efficient and experimentally convenient variation of the classical Robinson-Gabriel reaction. Cyclodehydration of 2-acylamino carbonyl compounds with Burgess reagent proceeds rapidly and cleanly under monomode microwave conditions. This new method compares favourably with activated triphenylphosphine-based cyclodehydration procedures[3] and avoids the sometimes troublesome removal of the triphenylphosphine oxide byproduct. Our method would be particularly suitable for high- throughput synthetic procedures. The broader scope of this procedure is currently under investigation.

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References and Notes

(1) Robinson, R. *J. Chem. Soc.* **1909**, *95*, 2167.
(2) Review: Turchi, I. J. In *The Chemistry of Heterocyclic Compounds*, 45; Wiley: New York, 1986; p1.
(3) (a) Bagley, M. C.; Buck, R. T.; Hind, S. L.; Moody, C. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 591. (b) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223. (c) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558 (d) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604. (e) Gordon, T. D.; Singh, J.; Hansen, P. E.; Morgan, B. A. *Tetrahedron Lett.* **1993**, *34*, 1901.
(4) Only two examples of the cyclodehydration of 2-acylamino aldehydes were found in the literature: Sen, P. K.; Veal, C. J.; Young, D. W. *J. Chem. Soc. Perkin Trans. 1* **1981**, 3053. (8.5% yield using $SOCl_2$). Wipf[3d] reported the preparation of a 2-monosubstituted oxazole by Dess-Martin periodinane oxidation of a 2-acylamino alcohol followed by $PPh_3/I_2/Et_3N$ induced cyclodehydration (17% overall).
(5) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744.
(6) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575.
(7) The usual reagent for the oxidative aromatization of oxazolines, NiO_2, provides oxazoles in moderate and variable yields, requires long reaction times and is sensitive to steric hindrence at C(5): (a) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961. (b) Evans, D. A.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L. Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497.
(8) (a) Meyers, A. I.; Tavares, F. X. *J. Org. Chem.* **1996**, *61*, 8207. (b) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W-C.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494.
(9) Shipton, M. R. *Synlett* **1992**, 491.
(10) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *Chem. Commun.* **1987**, 1625.
(11) Anelli, P. L.; Biffi, C.; Montanari, F; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.
(12) **1g,h** were obtained using ethyl acetate/water as the biphasic system. Use of dichloromethane/water tended to result in emulsion formation and concomitant degradation of the aldehydes.
(13) The quality of commercial Burgess reagent has been reported to be batch-dependent: Wipf, P.; Venkatraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659.

(14) Selected examples: (a) de la Hoz, A.; Moreno, A.; Vazquez, E. *Synlett*, **1999**, 608. (b) Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1253. (c) Danks, T. N. *Tetrahedron Lett*. **1999**, *40*, 3957. (d) Hoel, A. M. L.; Nielsen, J. *Tetrahedron Lett*. **1999**, *40*, 3941.

(15) Brain, C. T.; Loong, Y.; Oakley, P. J.; Paul, J. M. *Tetrahedron Lett*. **1999**, *40*, 3275.

(16) **2a-h** were characterized spectroscopically; where appropriate, (**2a-f**), data were in agreement with literature values.[2,3a]

(17) Typical procedure: the 2-acylamino carbonyl compound **1** (1 mmol) and Burgess reagent **5** were dissolved in dry THF (2 ml) in a screw-top Pyrex tube (16 x 100 mm) fitted with a PTFE septum. The reaction mixture was irradiated in a Labwell MW10 microwave apparatus (caution pressure develops). After cooling to room temperature in the microwave cavity, the reaction mixture was analysed by TLC/LC-MS. If starting material remained, additional Burgess reagent **5** was added and irradiation was repeated. When no starting material remained THF was removed *in vacuo* and the residue was applied to a short column of silica gel, eluting with hexane/ethyl acetate, to provide **2**.
Selected data: **2g**, colourless oil; ^{1}H nmr (400 MHz, DMSO) 8.22 (1 H, d, *J* 0.7, Oxaz 5-H), 7.74 (1 H, dt, *J* 10, 1.5, ArH), 7.56 (1 H, t, *J* 8, ArH), 7.45 (3 H, m, ArH), 7.37 (1 H, d, *J* 0.7, Oxaz 4-H), 7.22 (2 H, m, ArH), 7.12 (2 H, m, ArH); *m/z* (EI) 237 (M^+, 100%).
2h, yellow oil; ^{1}H nmr (200 MHz, $CDCl_3$) 7.89 (1 H, d, *J* 9, ArH), 7.71 (1 H, s, Oxaz 5-H), 7.26 (1 H, s, Oxaz 4-H), 7.12 (1 H, s, ArH) overlapping 7.10 (1 H, d, *J* 9, ArH), 2.67 (3 H, s, Me), 2.48 (3 H, s, Me); *m/z* (EI) 173 (M^+, 100%).

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