JOC*Note*

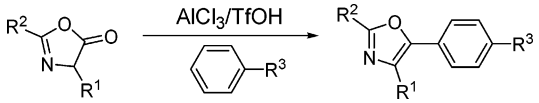
One-Pot Friedel−Crafts/Robinson−Gabriel Synthesis of Oxazoles Using Oxazolone Templates

Manasi Keni and Jetze J. Tepe*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

tepe@chemistry.msu.edu

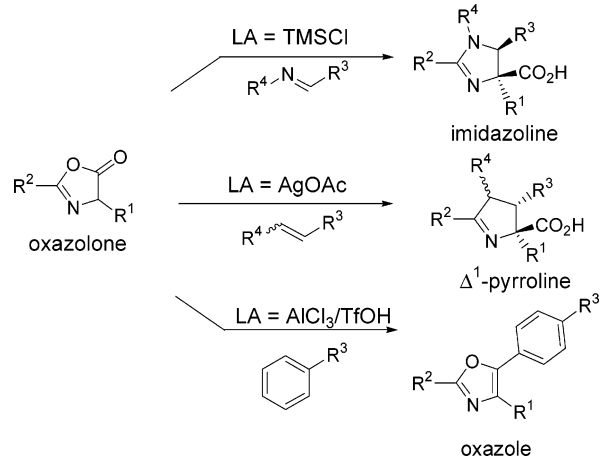
Received January 25, 2005



We report herein a one-pot synthesis of 2,4,5-trisubstituted oxazoles via a Friedel−Crafts/Robinson−Gabriel synthesis using a general oxazolone template. Treatment of the oxazolone template with a range of aromatic nucleophiles provided the highly substituted oxazoles in good yields.

The development of small molecular weight scaffolds containing a high degree of diversity has become a leading focus in modern drug discovery.[1] As part of our program to develop diverse classes of small molecule libraries containing potential biological properties, we have developed a substrate-controlled diversity-oriented synthesis (DOS) using a general oxazolone template. Recently, we reported the use of the oxazolone template for cycloaddition reactions with imines and alkenes to provide the corresponding imidazolines and Δ^1-pyrrolines.[2] As an extension of this approach, we report herein a one-pot synthesis of 2,4,5-trisubstituted oxazoles via a Friedel−Crafts/Robinson−Gabriel synthesis (Scheme 1). The oxazole nucleus is present in a wide variety of natural and unnatural biologically active compounds[3] and is a useful reagent in the synthesis of a range of biologically active scaffolds.[4,5] A number of methods exist

SCHEME 1. Substrate Controlled Diversity Synthesis of Heterocycles Using Oxazolones



in the literature for the synthesis of oxazoles;[5,6] however, due to its abundant representation as a synthetic and medicinal scaffold, new methods for the facile production of oxazoles continue to be of interest.[7] One of the oldest yet most versatile methods to generate 2,5-di- and 2,4,5-trialkyl-, aryl-, heteroaryl-, and alkyloxazoles is the Robinson−Gabriel cyclodehydration of 2-acylamino ketones.[8] The latter can be generated via an aluminum chloride mediated Friedel−Crafts acylations of oxazol-5-ones and aromatics.[9] In contrast, Friedel−Crafts acylations with the traditional acid chloride derivatives of amino acids are often cumbersome.[10]

We investigated the possibility of combining the Friedel−Crafts reaction and Robinson−Gabriel cyclodehydration reaction in a one-pot synthesis of 2,4,5-trisubstituted oxazoles using a general oxazolone template. After screening a small number of Lewis acids, aluminum chloride was found to be the most successful in producing the Friedel−Crafts products. The 2-acylaminoketones were subsequently evaluated for their ability to cyclize and dehydrate in situ to the corresponding oxazoles. A number of dehydrating agents were evaluated in combination with $AlCl_3$ for their ability to provide a one-pot oxazole synthesis (Table 1). We found that trifluoromethanesulfonic acid was the reagent of choice generating the desired product in a one-pot sequence with the aluminum chloride.

Other common dehydrating reagents used in Robinson−Gabriel cyclodehydration reactions are phosphorus

* Corresponding author. Phone: 517-361-9715. Fax: 517-353-1793.

(1) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58. (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613−618. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969. (b) Schreiber, S. L.; Nicolaou, K. C.; Davies, K. *Chem. Biol.* **2002**, *9*, 1−2. (b) Wipf, P.; Stephenson, C. R.; Walczak, M. A. *Org. Lett.* **2004**, *6*, 3009−3012.

(2) (a) Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* **2002**, *4*, 3533−3535. (b) Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, *9*, 1433−1440. (c) Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2004**, *126*, 12776−12777.

(3) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115−2134. (b) Lewis, J. R. *Nat. Prod. Rep.* **1995**, *12*, 135−163. (b) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 584−605.

(4) (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795−819. (b) Talley, J. J.; Bertenshaw, S. R.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Norman, B. H.; Rogier, D. J., Jr.; Zweifel, B. S.; Seibert, K. *Med. Res. Rev.* **1999**, *19*, 199−208. (c) Wasserman, H. H.; McCarthy, K. E.; Prowse, K. S. *Chem. Rev.* **1986**, *86*, 845−856.

(5) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3606.

(6) (a) Moody, C. J.; Doyle, K. J. *Prog. Heterocycl. Chem.* **1997**, *9*, 1−16. (b) Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132−7133. (c) Cunico, R.; Kaum, C. P. *J. Org. Chem.* **1992**, *57*, 6999−7000. (d) Houwing, H. A.; Wildeman, J.; van Leusen, A. M. *J. Heterocycl. Chem.* **1981**, *18*, 1133−1139.

(7) (a) Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593−3595. (b) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501−2504. (c) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165−1168. (d) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011−1014.

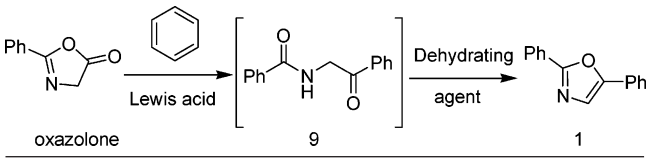
(8) (a) Robinson, R. *J. Chem. Soc.* **1909**, *95*, 2167. (b) Gabriel, S. *Ber.* **1910**, *43*, 1283.

(9) Katritzky, A. R. *Adv. Heterocycl. Chem.* **1965**, *4*, 82−84.

(10) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157−6163.

10.1021/jo0501590 CCC: $30.25
Published on Web 04/09/2005

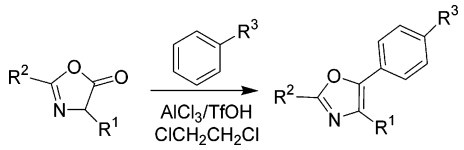
TABLE 1. Screening of Lewis Acids for One-Pot Friedel–Crafts/Robinson–Gabriel Synthesis



Lewis acid/dehydrating agent	intermediate **9**[a] (%)	product **1**[a] (%)
$AlCl_3$	85	0
$AlCl_3$/TfOH	0	76
TfOH	NR	NR
$AlCl_3$/TFAA	NR	NR
TFAA	NR	NR
$AlCl_3$/Tf_2O	NR	NR
Tf_2O	NR	NR
$AlCl_3$/P_2O_5	85	0
$AlCl_3$/$POCl_3$	85	0
BF_3·OEt_2/TfOH	NR	NR
P_2O_5·CH_3SO_3H/TfOH	NR	NR

[a] NR = no reaction.

TABLE 2. Yields of Oxazoles with Various Substitutions



no.	R^1	R^2	R^3	% yield
1	H	C_6H_5	H	76
2	H	$CH_2C_6H_5$	H	38
3	H	CH_3	H	55
4	CH_3	C_6H_5	H	81
5	CH_2 C_6H_5	C_6H_5	H	51
6	$CH(CH_3)_2$	C_6H_5	H	82
7	C_6H_5	C_6H_5	H	87
8	CH_3	C_6H_5	CH_3	65
9	CH_3	C_6H_5	OCH_3	78
10	H	C_6H_5	OCH_3	73
11	H	C_6H_5	C_6H_5	81
12	H	C_6H_5	Br	63
13	H	C_6H_5	NO_2	0

pentoxide, phosphorus oxychloride, trifluoroacetic anhydride, and triflic anhydride, which were all found to be unsuccessful in generating the oxazoles in this one-pot sequence (Table 1). The oxazolones were prepared from 2-acylamino acids by dehydration with 1-ethyl-3-(3′dimethylaminopropyl)carbodiimide·HCl (EDCI) or trifluoroacetic anhydride to provide the pure oxazol-5-ones in high yields.[11] The 2-acylamino acids were prepared via Schotten–Bauman-type cyclizations of amino acids.[12] The efficacy of various oxazol-5-ones, containing different substitutions at the C-2 (R2) and C-4 (R1) positions, to undergo this Friedel–Crafts/Robinson–Gabriel reaction with different aromatic substrates is illustrated in Table 2.

In the case of oxazoles with R^3 = H and R^3 = CH_3, dry benzene and toluene are used, respectively. Exposure of

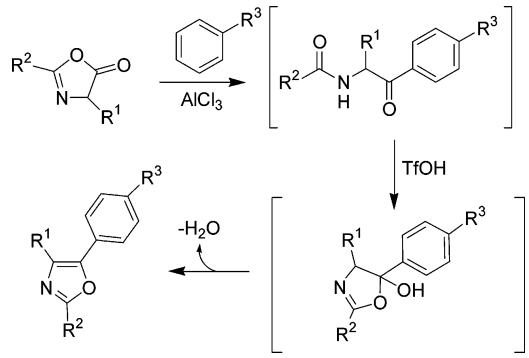
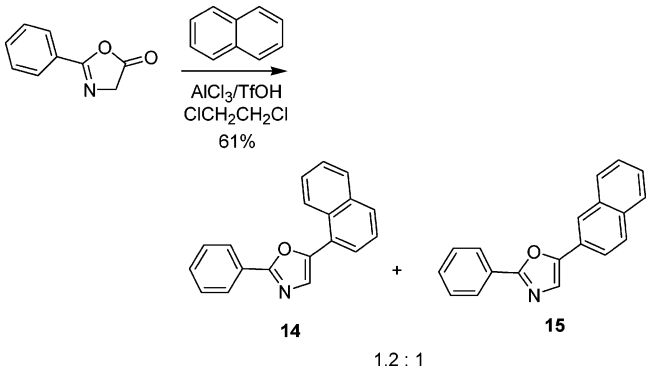


FIGURE 1. One-pot synthesis of oxazoles from oxazol-5-ones.

SCHEME 2. Synthesis of Naphthalene-Substituted Oxazoles



the oxazole template to naphthalene provided a 1:1.2 mixture (Scheme 2, 61% yield).

All reactions proceeded smoothly with various aromatic substrates in moderate to good yields (Table 1), with the exception of the electron-deficient nitrobenzene (Table 1, entry 13). Treatment of the oxazolones with $AlCl_3$ (3 equiv) with either benzene or toluene as solvent followed by the exposure of the reaction mixture to trifluoromethanesulfonic acid (10 equiv) resulted in the formation of the oxazoles. Alternatively, 1,2 dichloroethane was used as solvent with a stoichiometric quantity of the aromatic substrate.

The mechanism of the Robinson–Gabriel synthesis has been elucidated by oxygen-labeling studies.[13] A possible mechanism consistent with these studies involves the activation of the oxazolones by $AlCl_3$ followed by the nucleophilic addition of the aromatic substrate generating the 2-acylamino ketones in situ. Protonation of the aryl ketone by the superacid results in the formation of an electrophilic carbonyl carbon, which is attacked by the amide oxygen generating a five-membered dihydrooxazolol (Figure 1). Dehydration of the dihydrooxazolol subsequently forms the oxazole.

In summary, we report an efficient method of generating 2,4,5-trisubstituted oxazoles via a one-pot Friedel–Crafts/Robinson–Gabriel reaction using a general oxazolone template. This one-pot oxazole reaction adds to the repertoire of the Lewis acid mediated substrate-controlled diversity-oriented synthesis using the oxazolone template.

(11) (a) Chen, F. M. F.; Kuroda, K.; Benoiton, N. L. *Synthesis* **1979**, 230–232. (b) Mukerjee, A. K. *Heterocycles* **1987**, *26*, 1077–1097. (c) Ivanova, G. *Tetrahedron* **1992**, *48*, 177–186.

(12) Sonntag, N. O. V. *Chem. Rev.* **1953**, *52*, 237–416.

(13) Wasserman, H. H.; Vinick, F. J. *J. Org. Chem.* **1973**, *38*, 2407–2408.

Experimental Section

General Procedure for the Synthesis of Oxazoles. In the general procedure for this reaction, the solvent was chosen depending on the R^3 group. Dry benzene ($R^3 = H$) or dry toluene for $R^3 = CH_3$ was used as the solvent. Alternatively, 1,2-dichloroethane was used as solvent with a stoichiometric quantity of the aromatic substrate. A suspension of $AlCl_3$ (3 equiv) in either benzene or toluene was prepared. To this was added the oxazol-5-one dropwise at 0 °C. This solution was stirred at 0 °C for 0.5 h and then at rt overnight. After 12 h of stirring, triflic acid (TfOH) (10 equiv) was added at −78 °C. This solution was stirred at −78 °C for 1 h, after which time the solution was stirred at room temperature for 2 days. The reaction mixture was treated with ice-cold water and subsequently washed with sodium bicarbonate. The organic layer was separated and dried over sodium sulfate and concentrated in vacuo. The crude compound was then purified using column chromatography. Characterization data of two representative examples are shown below:

Oxazole **1**, 2,5-diphenyloxazole: ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.06 (2H, d, J = 7.4 Hz), 7.66 (2H, d, J = 7.6 Hz), 7.36−7.44 (6H, m), 7.28 (1H, t, J = 7.4 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 160.8, 145.7, 135.9, 129.1, 129.0, 128.7, 128.3, 127.7, 125.4, 126.5, 123.7; MS (EI) *m/e* 221.0 (100.0) (M^+); IR (cm^{-1}) 2924.46, 1491.16, 1444.87, 1134.29; mp 70−71 °C. Anal. Calcd for $C_{15}H_{11}NO$: C, 81.45; H, 4.98; N, 6.33. Found: C, 81.23; H, 4.41; N, 6.25.

Oxazole **4**, 4-methyl-2,5-diphenyloxazole: ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.09 (2H, d, J = 7.4 Hz), 7.69 (2H, d, J = 7.7 Hz), 7.42−7.49 (5H, m), 7.33 (1H, t, J = 7.4 Hz), 2.49 (3H, s); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 159.8, 145.6, 133.9, 131.0, 129.3, 128.9, 128.8, 127.7, 127.5, 126.3, 125.4, 33.9; MS (EI) *m/e* 235.1 (100.0) (M^+); IR (cm^{-1}) 2930.00, 1597.26, 1485.38, 1448.73, 1075.00; mp 78−80 °C. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.70; H, 5.53; N, 5.95. Found: C, 81.41; H, 5.20; N, 5.95.

Acknowledgment. We gratefully acknowledge the financial support provided by the American Cancer Society (RSG CDD-106972) and Michigan State University.

Supporting Information Available: Experimental procedures, IR, ^{1}H and ^{13}C NMR, and HRMS data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0501590