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# A Practical Approach to the Synthesis of 2,4-Disubstituted Oxazoles from Amino Acids

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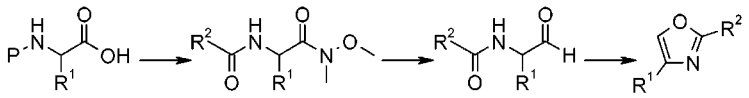
## ABSTRACT



**A new sequence for the synthesis of various 2,4-disubstituted oxazoles from α-amino acids is reported. The method is shown to be general and incorporates the reagent combination, triphenylphosphine/hexachloroethane, for cyclodehydration of intermediate α-acylamino aldehydes. Implementation of this reagent system for the conversion of α-acylamino ketones to oxazoles is briefly investigated.**

A typical progression of events following the discovery of a peptide fragment with activity in a biomolecular assay is the rational design of peptidomimetic surrogates providing enhanced stability and bioavailability. The mimetic ideally maintains binding elements and conformation in a rigid scaffold rendering a more druglike series for development. Heterocycles are commonly used, and oxazoles can be a particularly judicious choice as they incorporate the elements of the amide bond.[1] Oxazoles have been used both as a primary scaffold and as a component of the peptide fragment. A series of oxazole benzenesulfonamides have recently been introduced as $\beta$-3 adrenergic receptor agonists.[2] Another recent example explores dopamine receptor binding profiles of a series of phenyl oxazoles.[3] A progression of articles in 1993 from Sterling Winthrop described the incorporation of azoles into a dipeptide producing enhanced substance P antagonists.[4] Oxazoles are also common structural motifs in nature originating from post-translational modifications of serine and threonine residues in peptides.[5]

Our research required a suitable method for the facile production of a variety of oxazoles unsubstituted at the 5 position, with unrestricted potential for elaboration of the remaining sites from readily available starting materials. Subsequent carbanion formation at the open position would allow coupling of these heterocycles to a peptide fragment.[6] This paper describes our approach to the preparation of 2,4-disubstituted oxazoles, with a brief digression to alternative substitution patterns, and explores the efficiency of the combination of triphenylphosphine and hexachloroethane as a mild cyclodehydrating reagent.

A number of methods exist in the literature for the synthesis of oxazoles. However, preparation of 2,4-disubstituted oxazoles from acyclic precursors can be quite challenging. $\beta$-hydroxy amide-derived oxazolines, which can be dehydrogenated to the parent heterocycle using various reagents are a common synthetic precursor.[7] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), nickel peroxide, man-

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(1) There are over 1000 oxazoles represented in the MDDR database (MDL version of Drug Data Reports).

(2) Ok, H. O.; Reigle, L. B.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L. W.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Strader, C. D.; Tota, L.; Wang, P.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1531.

(3) Einsedeil, J.; Thomas, C.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2041.

(4) (a) Singh, J.; Gordon, T. D.; Earley, W. G.; Morgan, B. A. *Tetrahedron Lett*. **1993**, *34*, 211. (b) Gordon, T.; Hansen, P.; Morgan, B.; Singh, J.; Baizman, E.; Ward, S. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 915. (c) Gordon, T. D.; Singh, J.; Hansen, P. E.; Morgan, B. A. *Tetrahedron Lett*. **1993**, *34*, 1901.

(5) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep*. **1999**, *16*, 249.

(6) Relevance of these heterocyclic peptides as enzyme inhibitors is the subject of a future publication.

(7) Gant, T. G.; Meyers, A. I. *Tetrahedron*, **1994**, *50*, 2297 and references therein.

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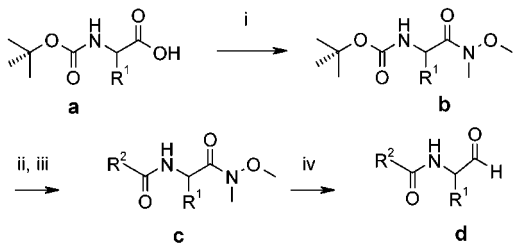
ganese dioxide, and phenylselenation/elimination have provided modest results for this oxidation. Recent modifications using copper bromide[8] or bromotrichloromethane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[9] have improved yields but require carboxy functionality at the 4 position. Hantzsch-type reactions of α-halocarbonyl derivatives with amides have also been used for the synthesis of 2,4-disubstituted oxazoles,[10] but the method is not as robust as for the synthesis of thiazoles. Other recent examples are inherently more specific in scope.[11] Our requirements for a robust, general method incorporating a large commercial reagent pool were not satisfied by these protocols.

Historically, one of the most useful procedures for the synthesis of oxazoles has been the cyclodehydration of α-acylaminoketones, or the Robinson−Gabriel synthesis.[12] Wipf has demonstrated that the difficult cyclodehydration of α-acylaminoaldehydes to oxazoles unsubstituted at the 5-position is possible using triphenylphosphine and iodine.[13] We recognized an opportunity for the synthesis of our targets using Wipf's modification, if a suitable method for preparation of the requisite aldehydes could be found. Our approach to the acyclic aldehydes (Scheme 1)[14] evolved as an adaptation of a method described by Buchanan for the synthesis of peptide thiazoles.[15] The Boc-protected acids (**a**) were converted to their Weinreb amides (**b**),[16] following activation with carbonyldiimidazole. Deprotection was generally accomplished by treatment with HCl in dioxane or ether or TFA in dichloromethane. The free amines were then acylated either by an acid chloride or an in situ generated acyl imidazole. Subsequent reduction with LAH[17] provided the desired aldehydes (**d**).

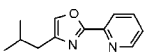
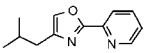
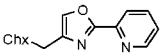
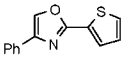
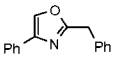
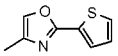
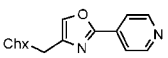
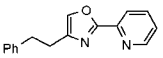
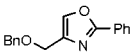
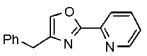
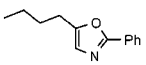
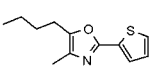
Cyclodehydration of the aldehydo amide (**d**) was initially attempted using triphenylphosphine and iodine. We experienced only moderate success with this reagent (Table 1, method A). More recent examples have employed the milder reagent system, triphenylphosphine and dibromotetrachloroethane to generate a bromo-oxazoline, which is subsequently dehydrohalogenated.[18] We used a similar reagent combination, triphenylphosphine and hexachloroethane (Table 1,

**Scheme 1**[a]




[a] Key: (i) carbonyldiimidazole, *N*-methyl-*O*-methylhydroxylamine hydrochloride, $CH_2Cl_2$; (ii) HCl, ether; (iii) $R^2$ acid chloride, TEA, $CH_2Cl_2$ or $R^2$ acid, carbonyldiimidazole, pyridine, $CH_2Cl_2$; (iv) LAH, THF.

**Table 1.** Conversion of α-acylamino Aldehydes to Oxazoles[a]

| entry/ method | | time (hr) 25°C | time (hr) 50°C | yield (%) |
|---|---|---|---|---|
| **1**/A[b] |  | 1 | 0 | 14 |
| **1**/B |  | 2 | 0 | 76 |
| **2**/A |  | 1.5 | 0 | 37 |
| **3**/C |  | 1 | 0 | 79 |
| **4**/C |  | 44 | 4 | 62[c] |
| **5**/C |  | 16 | 0 | 57 |
| **6**/C |  | 15 | 1 | 76 |
| **7**/C |  | 2 | 2 | 61 |
| **8**/C |  | 1 | 0 | 51[d] |
| **9**/B |  | 1 | 0 | 70 |
| **10**/B |  | 1.5 | 0 | 94 |
| **11**/B |  | 1.5 | 0 | 81 |
| **12**/C |  | 1 | 20 | 51 |
| **13**/C |  | 4 | 0 | 91 |

[a] All yields are isolated products. Reaction mixtures were heated if conversion was incomplete after the designated time at room temperature. [b] See the Supporting Information for examples of the methods. [c] 13% of the chloro-oxazoline was also isolated. [d] 24% of the chloro-oxazoline was also isolated.

(8) (a) 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) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331. (b) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.

(10) Liu, P.; Celatka, C. A.; Panek, J. S.; *Tetrahedron Lett.* **1997**, *38*, 5445.

(11) (a) Hermitage, S. A.; Cardwell, K. S.; Chapman, T.; Cooke, J. W. B.; Newton, R. *Org. Process Res. Dev.* **2001**, *5*, 37. (b) Lee, J. C.; Song, I.-G. *Tetrahedron Lett.* **2000**, *41*, 5891. (c) Pei, W.; Li, S.; Nie, X.; Li, Y.; Pei, J.; Chen, B.; Wu, J.; Ye, X. *Synthesis* **1998**, 1298. (d) Swaminathan, S.; Singh, A. K.; Li, W.-S. Venit, J. J.; Natalie, K. J., Jr.; Simpson, J. H.; Weaver, R. E.; Silverberg, L. J. *Tetrahedron Lett.* **1998**, *39*, 4769.

(12) Robinson, R. *J. Chem. Soc.* **1909**, *95*, 2167.

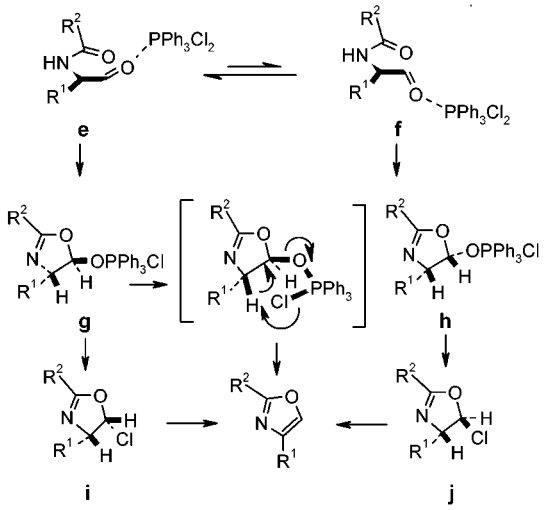
(13) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.

(14) Due to price/availability, only the nonracemic (S) amino acids were used in all cases. Integrity of the asymmetric center was not confirmed for the intermediates (Schemes 1−4), and therefore, absolute stereochemistry is not depicted. However, literature precedence would suggest aldehydes **d** and ketones **m** would be nonracemic. For a review of Weinreb amide chemistry, see: Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15−40. (b) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339* 517−524.

(15) Buchanan, J. L.; Mani, U. N.; Plake, H. R.; Holt, D A. *Tetrahedron Lett.* **1999**, *40*, 3985.

methods B, C).[19] This in situ generated phosphonium halide provided greatly enhanced yields and cleaner reactions with rapid oxazole formation. However, reaction intermediates were observed. Specifically, the presence of chloro-oxazoline adducts (Scheme 2) were monitored by TLC and, in certain cases, were isolated from the reaction mixtures.

**Scheme 2**

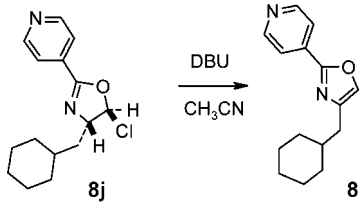


In an attempt to develop a baseline understanding of the details of this process, we carried out a series of reactions to study the formation of **6** (Table 1) using various bases (or in the absence of base) and varying the order of addition of the four components. All test reactions were run at room temperature in acetonitrile or a mixture of acetonitrile and dichloromethane. Reactions were monitored by TLC, and all components were isolated from the plates and subjected to mass analysis. Our observations indicated rapid consumption of the aldehyde, generally within 1 min, and concurrent formation of the oxazole with two additional adducts. Triphenylphosphine oxide was also formed in the process. Mass analysis of the adducts suggested two independent chloro-oxazoline intermediates. Consistently, the minor adduct was consumed quickly in the presence of base (within 5−10 min), while the major adduct persisted for several hours. To our surprise, oxazole formation was consistently rapid in the complete absence of base, and similar ratios of the three aldehyde-derived components were observed with or without base at the initial time point of 1 min.[20] Additionally, in the absence of base, the two intermediates persisted for up to 24 h in the reaction mixture. Subsequent introduction of pyridine initiated rapid consumption of the minor adduct and a much slower disappearance of the major chloro-oxazoline intermediate as before. The two intermediates were isolated by flash chromatography but decomposed partially to the oxazole and partially to other components on drying under vacuum. It was also established that pure oxazole was not converted to either of the two adducts under the reaction conditions. These observations indicate that oxazole formation proceeds through various pathways. We have suggested a potential mechanistic explanation of these results (Scheme 2).

Activation of the aldehyde by the phosphine reagent initiates an allowed intramolecular 5-*exo*-*trig* cyclization.[21] Stereoinduction by $R^1$ may favor conformation **e**, leading to **g**, which may progress directly to oxazole via syn elimination, through a cyclic six-membered transition state. Alternatively, this intermediate can undergo decomposition of the oxyphosphorane with inversion[22] providing the transient minor chloro-oxazoline adduct **i**, which is readily converted to oxazole in the presence of base by anti elimination (E2). Cyclization from the alternate conformation **f** provides intermediate **h**, which does not have the option of syn elimination through the cyclic transition state.[23] Decomposition with inversion of **h** to the halide produces the major, long-lived adduct, **j**. This intermediate proceeds through what must be a higher energy syn elimination of HCl to the final product.[24]

Certain other examples were also analyzed by TLC/MS during the course of the reaction. For examples **7** and **8** (Table 1), both intermediates as well as the oxazole were observed and confirmed by mass analysis. For **4**, the long-lived adduct **4j** was isolated from the reaction following unsuccessful attempts to convert it to the oxazole using an extended reaction time. However, it also proved to be too unstable for complete purification and characterization. For example **8**, the short-lived adduct **8i** lasted only 20−30 min, in typical fashion. Also consistently, the second intermediate persisted and in this case proved to be remarkably stable. Following purification, **8j** was analyzed extensively by NMR, including HMBC and NOESY. The results are consistent with the suggested relative stereochemistry. This adduct could be converted to the oxazole following treatment with DBU in acetonitrile at room temperature for several days (Scheme 3).

**Scheme 3**

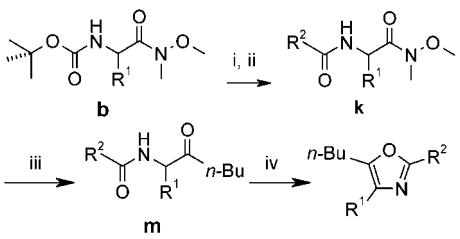


This preliminary analysis provided us with a working hypothesis.[25] Subsequently, we decided to briefly explore the practicality of this reagent combination for the cyclodehydration of α-acylamino ketones, also derived from the

(16) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(17) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676.
(18) (a) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157. (b) Wipf, P.; Lim, S. *J. Am. Chem. Soc*. **1995**, *117*, 558. (c) Yokokawa, F.; Asano, T.; Shioiri, T. *Org. Lett*. **2000**, *2*, 4169.
(19) Appel, R.; Willms, L. *Chem. Ber*. **1979**, *112*, 1064.
(20) It has been reported that no reaction occurs in the absence of base when the reagent system triphenylphosphine/iodine is used.[13]

Weinreb amide[10] by reaction with an alkyllithium reagent[26] (Scheme 4) In this case, oxazole formation was sluggish,

**Scheme 4**[a]




[a] Key: (i) HCl, ether; (ii) $R^2$ acid chloride, TEA, $CH_2Cl_2$, or $R^2$ acid, carbonyldiimidazole, pyridine, $CH_2Cl_2$; (iii) *n*-BuLi, THF; (iv) $Ph_3P$, $C_2Cl_6$, pyridine, $CH_3CN$.

and the acyclic ketones persisted much longer under the reaction conditions. For **12**, only the ketone **12m** was identified by TLC after 1 h at room temperature. Complete conversion to the oxazole was observed after heating at 50 °C for 20 h.[27] Formation of **13** occurred at room temperature, but 4 h was required for complete consumption of the ketone **13m**. Interestingly, the ketones apparently proceeded directly to the oxazole, and no chloro-oxazoline intermediates were observed. At 3 h, TLC/MS of the reaction for **13** revealed the starting ketone, the oxazole and triphenylphosphine oxide as the only detectable species. This would be expected, as decomposition of the oxyphosphorane to the halide with inversion should not occur at the tertiary center.

An account of all examples is provided in the table (Table 1). Specific examples of the methods are described in the Supporting Information.

In summary, a novel and general approach to the synthesis of 2,4-disubstituted oxazoles that offers diversity and utilizes readily available starting materials has been reported. A limited investigation of the cyclodehydration reaction using triphenylphosphine and hexachloroethane is described, and various pathways leading to oxazole formation have been suggested. Cyclodehydration of ketone adducts using this same reagent combination is also briefly explored.

**Acknowledgment.** We thank Professor Peter Wipf at the University of Pittsburgh for his helpful advice in the case of cyclodehydration reagents.

**Supporting Information Available:** General methods, experimental procedures for the preparation of **2** (method A), **1** (method B), **6** (method C), preparation of the Weinreb amide **6b**, amine deprotection and formation of amides **6c** (via acid chloride) and **5c** (via acyl imidazole), conversion of the Weinreb amide to aldehyde **6d**, conversion of the Weinreb amide to ketone **13m**, and characterization data for **1**−**4**, **4j**, **5**, **6**, **6i**,**j**, **7**, **7i**,**j**, **8**, **8i**,**j**, and **9**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL020092S

(21) It has been shown previously by isotopic labeling, that the amide oxygen is retained in the product. Wasserman, H. H.; Vinick, F. J. *J. Org. Chem.* **1973**, *38*, 2407.

(22) (a) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1970**, *35*, 1627. (b) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.

(23) We anticipate that anti elimination of **h** directly to oxazole, a process observed to occur in the absence of base, would be much slower than conversion to the halide, **j**.

(24) A rate preference factor of 9 for anti elimination of *cis*-2-phenylcyclopentyl tosylate over syn elimination of the corresponding diastereomer has been documented. See DePuy, C. H.; Morris, G. F.; Smith, J. S.; Smat, R. J. *J. Am. Chem. Soc.* **1965**, *87*, 2421.

(25) For an alternative mechanistic proposal using triphenylphosphine and iodine, see 13.

(26) Cyclodehydration of α-acylaminoketones using triphenylphosphine and iodine has been reported. See, for example: (a) Haberhauer, G. Somogyi, L. Rebek, J. Jr. *Tetrahedron Lett.* **2000**, *41*, 5013. (b) Wipf, P.; Cunningham, A.; Rice, R. L.; Lazo, J. S. *Bioorg. Med. Chem.* **1997**, *5*, 165.

(27) The reaction was not analyzed during the 20 h at 50 °C. Therefore, less time may have been required for completion.