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LANTHANIDE CATALYZED SYNTHESIS OF β-HYDROXYL AMIDES

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ABSTRACT: Lanthanide (III) chloride improved the reaction of carboxylic esters with β-amino alkoxides (generated *in situ* from β-amino alcohols) and produced β-hydroxyl amides under mild conditions, and in high yields.

β-Hydroxyl amides are important intermediates among the protocols that were developed for the synthesis of 2-oxazolines and bisoxazolines.[1] Oxazolines are present in many biologically active natural products.[2] The synthetic utility of oxazolines[3] and bisoxazolines, particularly in the area of transition metal catalyzed asymmetric synthesis[4] has been demonstrated and remains a topic of recent interest. Intramolecular cyclization of β-hydroxyl amides has been reported

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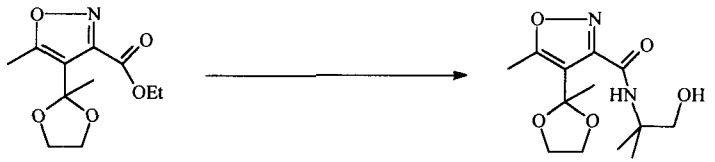
using powerful hydroxyl activating reagents. Recent methods for the cyclization of β-hydroxyl amides to 2-oxazolines include diethylamidosulfur trifluoride (DAST),[5] methyl N-(triethylammoniosulfonyl) carbamate (Burgess reagent),[6] the Mitsunobu reaction,[7] Hendrickson reagent.[8] Many these routes to 2-oxazolines are attractive, due to the mild reaction conditions, tolerance toward other functional groups, and high yields. The method most often employed for the formation of the β-hydroxyl amide, however, is the Shotten-Bauman acylation of β-amino alcohols with acyl chlorides under basic conditions. Preparation of acyl chlorides, from carboxylic acids requires an additional step, harsh conditions, and in many cases an additional purification which lowers the overall yield. For simple β-amino alcohols, the use of triphenylphosphine-CCl_4-triethylamine reagent represents an alternative choice, the carboxylic acids can be directly transformed to the corresponding 2-oxazolines in one step.[9] If the amino group in the β-amino alcohols is sterically encumbered, as in the case of most chiral β-amino alcohols, this method could not be successfully adapted, because the hydroxyl group was partially phosphorylated to the corresponding O-triphenylphosphonium chloride and/or acid chlorides, this resulted in the formation of aziridine intermediates which after N-acylation and rearrangement gave a mixture of the corresponding 4- and 5-substituted oxazolines.

We wish to report a general method for the preparation of β-hydroxyl amides by using carboxylic esters and amino alcohols, which was catalyzed by lanthanide chloride, the product β-hydroxyl amides can be synthesized in high

Scheme 1



1 **2**

Table 1. Optimization of the Reaction Conditions in Scheme 1

Entry	Lanthanide	Base*	Solvent/Time	Yield(%)
1		Excess amino alcohol/12 h		Decomposition**
2	0.10eq. $SmCl_3$	nBuLi	Toluene/12 h	46
3	0.10eq. $SmCl_3$	nBuLi	CH_2Cl_2/45min.	95
4	0.01eq. $SmCl_3$	nBuLi	CH_2Cl_2/1 h	93
5	0.0025eq. $SmCl_3$	nBuLi	CH_2Cl_2/45min.	51
6	0.10eq. $SmCl_3$		CH_2Cl_2/12 h	No reaction
7		nBuLi	CH_2Cl_2/1 h	Decomposition

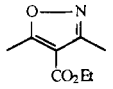
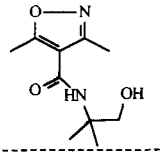
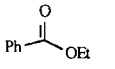
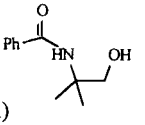
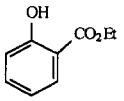
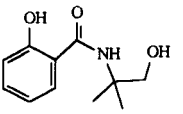
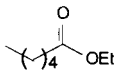
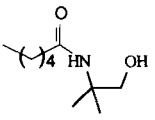
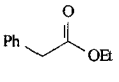
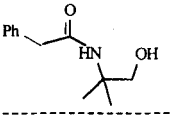
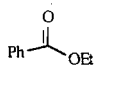
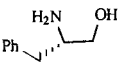
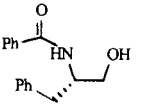
* Using 1.05 eq. nBuLi, 1.1 eq. 2-amino-2-methyl-1-propanol; except in entry 2 is 2.2 eq. nBuLi and 2.5 eq. 2-amino-2-methyl-1-propanol. ** mainly is 2-acetyl--3-oxobutanenitrile.

yield under relatively mild conditions (*vide infra*). In order to optimize the experimental protocol, we carefully examined a model reaction, illustrated in Scheme 1 under various conditions summarized in Table 1. Ethyl 4-[1-(1,3-dioxolanyl)-ethyl]-5-methyl-isoxazole-3-carboxylate (**1**) is of interest as an entry into analogues of the central nervous system pro-drug, Amino-methylisoxazole propionic acid (AMPA). During the course of work directed towards a general

approach to AMPA analogues, the amide (**2**) was required. The correspounding isoxazole-3-carboxylic acids is usually not stable at room temperature[10]. Refluxing this ester with excess 2-methyl-2-amino-propanol did not produce the corresponding β-hydroxyl amide (Table 1, Entry 1), in contrast to the many examples reported which lack the functional complexity of our target molecule.[11] Using the direct method for the synthesis of 2-oxazolines that we have recently reported [0.1 equivalent anhydrous lanthanide (III) chloride and refluxing toluene],[12] however, only produced low yields of the amide (**2**) as shown in Table 1, Entry 2. High yields of the amide were obtained upon refluxing for 1h in methylene chloride with one equivalent of lithium amino alkoxide (which was prepared *in situ*) and a catalytic amount of samarium chloride (0.01 eq, Table 1, Entry 4). In contrast, when the mole equivalent of $SmCl_3$ was reduced to 0.25% the yield was lowered (Table 1, Entry 5), which we attributed to the formation of the decomposition product 2-acetyl 3-oxobutanenitrile as evidenced by tlc. It was also found that both catalytic amounts of lanthanide chloride and the base (though not necessarily n-butyllithium) were required factors for success in the reaction, absence of either one resulted in either recovery of unreacted starting material (Table 1, Entry 6) or decomposition (Table 1, Entry 7).

This method can be used to transform a variety of carboxylic esters to corresponding β-hydroxyl amides as shown in Table 2. Simple esters including hetero-aromatic (Table 2, Entry 1), aromatic (Table 2, Entry 2), or aliphatic esters

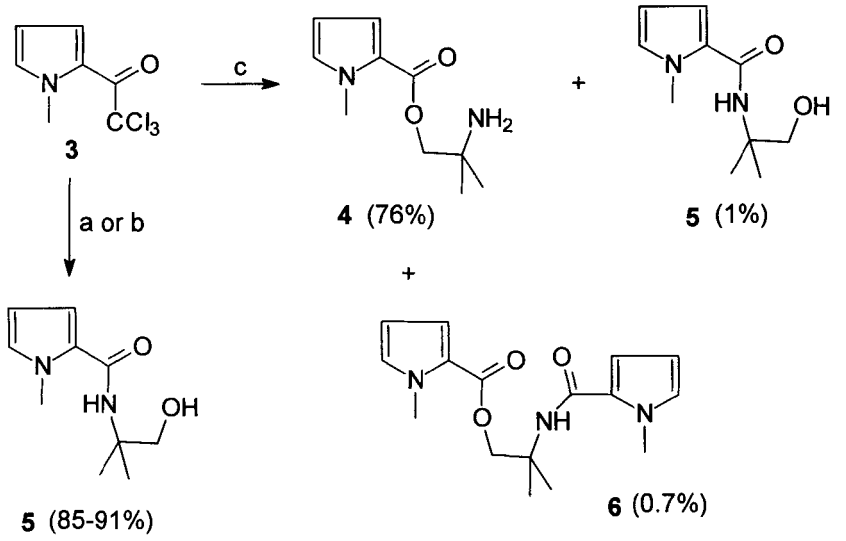
Table 2. Lanthanide Catalyzed Synthesis of β-Hydroxyl Amides From Esters*

Entry	Carboxylic ester	Amino alcohol	Lanthanide (Solvent, Time)	Product	Yield(%)
1			0.01eq. $SmCl_3$ (CH_2Cl_2, 48h)		72
2			0.01eq. $LaCl_3$ (CH_2Cl_2, 24h) 0.01eq. $LaCl_3$ (CH_2ClCH_2Cl, 1h)		100 100
3			0.01eq. $SmCl_3$ (CH_2ClCH_2Cl, 1h)		88
4			0.01eq. $LaCl_3$ (CH_2Cl_2, 24h)		99
5			0.01eq. $LaCl_3$ (CH_2Cl_2, 12h)		95
6			0.01eq. $LaCl_3$ (CH_2Cl_2, 24h)		92

* Using 1.1 eq. amino alcohol and 1.05 eq. nBuLi, all reactions are being reflexed in the indicated solvent.

(Table 2, Entries 4 and 5), were easily transformed in excellent yield, and additional hydroxyl groups do not disturb the reaction (Table 2, Entry 3). Higher temperature (refluxing 1,2-dichloroethylane, 80 °C) shortens the reaction time with no apparent change in yield (shown for ethyl benzoate, Table 2, Entry 2).

Scheme 2



a) 0.01 eq. $SmCl_3$, 1.05 eq. nBuLi, 1.1 eq. 2-amino-2-methyl-1-propanol, CH_2Cl_2, 12 h, 91%. b) 1.05 eq. nBuLi, 1.1 eq. 2-amino-2-methyl-1-propanol, CH_2Cl_2, 12 h. 85%. c) 0.1 eq. K_2CO_3, 1.1 eq. 2-amino-2-methyl-1-propanol, Toluene, 12 h.

Enantiomerically pure amino alcohols can be transformed to the corresponding β-hydroxyl amides in good yield without racemization (Table 2, Entry 6).

To further demonstrate the utility of this method, the reaction of the lithium amino alkoxide with 1-methyl-2-trichloroacetyl pyrrole (**3**) in the presence of catalytic amounts of lanthanide chloride was explored as shown in Scheme 2, With the lithium salt of 2-methyl-2-amino-propanol the reaction is facile with one percent samarium chloride to transform the trichloroacetyl group to the β-hydroxyl amide (**5**). Since the trichloroacetyl can be easily introduced onto a

hetero-aromatic ring,[14] Reactions with conditions optimized for the 2-hydroxyamide, produced the amide (**5**) in excellent yield. This method will offer a new way to attach β-hydroxylamides onto the desired compounds.

In contrast with the usual observation that the β-amino esters are not stable, it was interesting to note that the corresponding β-amino ester (**4**) can be formed from the 2-trichloroacetyl pyrrole (**3**) when the reaction was run at higher temperature in a non-polar solvent such as toluene, with anhydrous potassium carbonate as the base. The metal cations are likely key to this chemical selectivity. Also observed were the bis pyrrole β-ester amide (**6**, 0.7%) togeher with β-hydroxyl amide (**5**, 1%). This demonstrated that the competition between the amino and hydroxyl group can be controlled by choice of the reaction conditions.

We continue to explore the use of lanthanide catalysts in organic synthesis, and will report on our progress in due course.

Experimental Section

Mass spectra were obtained on a VG 7070 GC/MS with model 11/250 data system. The ^{1}H and ^{13}C NMR were obtained on a Bruker 200 at 200 MHz multi-nuclear and/or an IBM NR300 at 300 MHz FT-NMR and are reported in ppm. IR spectra were obtained on a DigiLab Qualimatic IR spectrophotometer as

neat oils on KBr plates and are reported in cm^{-1}. All reactions were performed under an inert atmosphere of nitrogen. All solvents were dried and distilled before use. n-Butyllithium reagent was titrated using standard methods. Preparative thin-layer chromatography was performed on a Harrison Associates Chromatotron with silica gel.

General procedure. A 25 mL round bottom flask was charged with anhydrous samarium chloride (0.01 mmol) and dry methylene chloride (10 mL). Then 2-methyl-2-amino-1-propanol (1.1 mmol) was added with a syringe. The reaction flask was stirred under nitrogen until a milk white suspension was formed. The flask was then cooled in an ice-water bath, n-butyl lithium (1.05 mmol) was added dropwise with a syringe. The mixture was stirred for 15 minutes at this temperature, then was allowed to warm to room temperature and brought to reflux. A carboxylic ester (1.0 mmol) was added with a syringe, then refluxing was continued until the starting ester disappeared as monitored by tlc, this usually required refluxing for 12 hours. The reaction mixture was cooled to room temperature, chloroform (20 mL) was added and the mixture washed with brine (3×10 mL). The aqueous solution was extracted with chloroform (10mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and evaporated to produce the product. This product was usually of sufficient purity for use in subsequent reactions. Further purification can be easily carried out by either flash or radial chromatography, or flash distillation with a Kugelrohr apparatus, as appropriate.

N-(2-hydroxyl-1,1-dimethylethyl) 4-[1-(1,3-dioxolanyl)-ethyl]-5-methyl-isoxazole-3-carboxamide (**2**). Kugelrohr distillation: yellowish oil, 108 °C (bath temperature)/0.11 mmHg. ^{1}H-NMR ($CDCl_3$) 7.09 (br, 1H, NH), 4.18 (t, 2H, J = 8Hz, CH_2), 4.04 (m, 2H, CH_2), 3.86 (m, 2H, CH_2), 3.70 (t , 1H, J = 8Hz, OH), 2.50 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.39 (s, 6H, CH_3); ^{13}C-NMR ($CDCl_3$) 167.47, 160.27, 157.35, 116.43, 105.47, 69.32, 64.63, 56.80, 26.79, 24.38, 12.10; EIMS *m/z* (relative intensity) 284 (M^+, 8), 268 (3), 252 (100), 208 (15), 169 (13), 154 (25), 126 (31); $C_{13}H_{20}N_2O_5$ [$(M+1)^+$] requires 285.1450, HRCIMS found: 285.1439.

N-(2-hydroxyl-1,1-dimethylethyl) 3,5-dimethyl-isoxazole-3-carboxamide (Table 2, Entry 1). obtained as an oil which crystallized on standing. mp. 42 - 43 °C (lit.[15] 42 - 43 °C). ^{1}H-NMR($CDCl_3$) 5.8 (br, 1H), 4.1 (br, 1H), 3.6 (s, 2H), 2.6 (s, 3H), 2.4 (s, 3H), 1.4 (s, 6H).

N-(2-hydroxyl-1,1-dimethylethyl) benzamide (Table 2, Entry 2). mp. 90 - 92 °C (lit.[16] 88 - 90 °C). ^{1}H-NMR ($CDCl_3$) 7.34 - 7.73 (m, 5H, C_6H_5), 6.61 (br, 1H, NH), 5.21 (br, 1H, OH), 3.62 (s, 2H, CH_2), 1.39 (s, 6H, CH_3); ^{13}C-NMR ($CDCl_3$) 168.54, 134.88, 131.48, 128.48, 126.94, 70.52, 56.16, 24.29.

N-(2-hydroxyl-1,1-dimethylethyl) 2-hydroxylbenzamide (Table 2, Entry 3). The reaction mixture was extracted with water (3×10mL), then the aqueous layers were washed with chloroform, acidified with 1M HCl to pH < 7,

extracted with chloroform (3×10mL), The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to produce the desired product as a yellowish oil, 98 - 100 °C/0.1 mmHg (lit.[17] 100 °C/0.1 mmHg). ^{1}H-NMR ($CDCl_3$) 11.90 (br, 1H, OH), 7.32 (m, 2H, Aromatic), 6.88 (m, 1H, Aromatic), 6.76 (m, 1H, Aromatic), 6.49 (br, 1H, NH), 3.61 (s, 2H, CH_2), 1.36 (s, 6H, CH_3); ^{13}C-NMR ($CDCl_3$) 170.40, 161.19, 134.23, 125.93, 118.79, 118.59, 114.74, 70.11, 56.31, 24.25.

N-(2-hydroxyl-1,1-dimethylethyl) Hexanamide (Table 2, Entry 4). A colorless oil, 65 - 67 °C/0.2 mmHg (lit.[18] 66 - 68 °C/0.2 mmHg). ^{1}H-NMR ($CDCl_3$) 5.92 (br, 1H, NH), 5.20 (br, 1H, OH), 3.43 (s, 2H, CH_2), 2.05 (t, J = 7.4, 2H, CH_2), 1.47 (m, 2H, CH_2), 1.16 (m, 10H, $2CH_2$, $2CH_3$), 0.78 (t, J = 6.5, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) 174.44, 70.79, 55.87, 37.01, 31.20, 25.41, 24.46, 22.26, 13.80.

N-(2-hydroxyl-1,1-dimethylethyl) benzeneacetamide (Table 2, Entry 5). White solid, mp. 77 - 78 °C, (lit.[18] 78 - 80 °C). ^{1}H-NMR ($CDCl_3$) 7.27 (m, 5H, Aromatic), 5.72 (br, 1H, NH), 4.95 (br, 1H, OH), 3.54 (s, 2H, $2CH_2$), 1.20 (s, 6H, $2CH_3$); ^{13}C-NMR ($CDCl_3$) 172.17, 134.84, 129.19, 128.99, 127.37, 70.5 1, 56.17, 44.09, 24.49.

N-Benzoyl-L-phenylalaniol (Table 2, Entry 6). mp. 170 - 172 °C. ^{1}H-NMR (DMSO-d_6) 8.20 (d, 1H), 7.80 (m, 2H), 7.46 (m, 3H), 7.19 (m, 5H), 4.88 (t,

1H), 4.18 (m, 1H), 3.50 (m, 2H), 2.91 (m, 2H); ^{13}C-NMR (DMSO-d_6) 167.15, 140.22, 136.50, 131.41, 130.18, 128.89, 128.74, 128.00, 126.72, 63.50, 54.37, 37.67. $[\alpha]^{20}_D$ = -62.8° (*c* = 0.55, MeOH, lit.[19] -62.4°).

(2-amino-2-methylpropanyl) 1-methyl-pyrrole-2-carboxylate (4). Anhydrous potassium carbonate (27.6 mg, 0.2 mmol), 1-methyl-2-trichloroacetyl pyrrole (453.0 mg, 2.0 mmol) and 2-amino-2-methyl-1-propanol (0.21 mL, 2.2 mmol) were placed in a 25 mL round bottom flask, and 10 ml dry toluene was added. The mixture was refluxed under nitrogen for 12 hours. Then cooled to room temperature and chloroform (20 mL) was added. The mixture was washed with brine (3×10 mL), the aqueous layer was extracted with chloroform (3×15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtrated, and concentrated. The resulting mixture was separated by radial chromatography (silica gel; hexane, ethyl acetate, methanol) to produce 297.0 mg product (**4**) as a yellowish oil (76%), which crystallized on standing, mp. 106 - 108 °C. IR 3340, 3090, 2945, 1690, 1400, 1232, 1100, 727; ^{1}H-NMR ($CDCl_3$) 1.18 (s, 6H, CMe_2), 1.90 (br, 2H, NH_2), 3.91 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 6.10 (dd, 1H, J = 2.6, 3.9Hz), 6.78 (t, 1H, J = 2.1, 2.3Hz), 6.96 (dd, 1H, J = 1.8, 4.1Hz); ^{13}C-NMR ($CDCl_3$) 161.10, 129.70, 117.84, 107.93, 72.84, 49.83, 36.87, 27.15; EIMS *m/z* (relatively intensity) 196 (M^+, 5), 165 (32), 108 (100); $C_{10}H_{16}N_2O_2$, (M^+) requires 196.1212, CI-HRMS Found: 196.1211. Along with 2.0 mg product **6** (0.7%), and 34 mg product **5** (1%).

N-(1,1-dimethyl-2-hydroxyethyl) 1-methyl-pyrrole-2-carboxamide (5). A yellowish oil, crystallized on standing, mp. 90 - 91 °C (lit. [20] 91 - 92 °C). IR 3300, 2930, 1595, 1510, 1385, 1243, 1040, 887, 715; ^{1}H-NMR 1.36 (s, 6H, CMe_2), 3.63 (s, 2H, CH_2), 3.90 (s, 3H, CH_3), 5.10 (br, 1H, OH), 5.95 (br, 1H, NH), 6.06 (dd, 1H, J = 2.6, 3.9Hz), 6.78 (t, J = 2.1, 2.3Hz), 6.96 (dd, 1H, J = 1.8, 4.1Hz); ^{13}C-NMR ($CDCl_3$) 162.84, 128.24, 125.61, 111.92, 107.13, 71.02, 56.09, 36.67, 24.75.

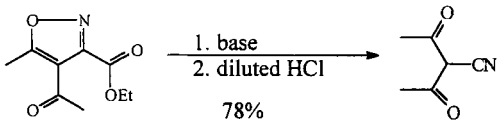
N-[2-(1-methylpyrrole-2-carbonyl)-hydroxyl-1,1-dimethyl]-ethyl 1-methyl-pyrrole-2-carboxylic amide (6). A yellowish oil. ^{1}H-NMR($CDCl_3$) 1.52 (s, 6H, CMe_2), 3.92 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 6.05 (dd, 1H, J = 2.6, 3.9Hz), 6.50 (dd, 1H, J = 1.8, 1.5, 4.0Hz) 6.68 (t, 1H, J = 1.8, 2.6Hz), 6.81 (t, 1H, J = 2.1Hz), 6.98 (dd, 1H, J = 1.8, 3.9Hz); ^{13}C-NMR ($CDCl_3$) 161.83, 161.41, 129.95, 127.69, 126.50, 122.10, 118.21, 111.28, 108.05, 106.92, 69.51, 53.93, 36.92, 36.71, 24.03; EIMS *m/z* (relatively intensity) 303 (M^+, 1), 165 (24.6), 108 (100), 80 (6.7); $C_{16}H_{21}N_3O_3$, (M^+) requires 303.1583, CI-HRMS Found: 303.1580.

References

1. For recent examples, see: a) Gant, T. G.; Noe, M. C.; Corey, E. J., *Tetrahedron Lett.*, **1995**, *36*, 8745. b) Lafargue, P.; Guenot, P.; Lellouche, J.-P., *Synlett.* **1995**, 171. c) Sund, C.; Ylikoski, J. and Kwiatkowski, M., *Synthesis,* **1987**, 853. d) Park, J.; Lee S.; Ahn. K. H. and Cho. C.-W.,

Tetrahedron Lett., **1995**, *36*, 7263. e) Hoveyda, H. R.; Karunaratne, V.; Rettig, S. J. and Orvig, C., *Inorg. Chem.* **1992**, *31*,5408.

2. Carmeli, S. C.; Moore, R. E.; Patterson, G. M. L., *J. Am. Chem. Soc.*, **1990**, *112*, 8195.
3. Grant, T. G.; Meyers, A. I., *Tetrahedron*, **1994**, *50*, 2297.
4. For recent examples, see: a) Wu, J. H.; Radinov, R. and Porter, N. A., *J. Am. Chem. Soc.*, **1995**, *117*, 11029. b) Cozzi P. G.; Floriani, C., *J. Chem. Soc. Perkin Trans. I*, **1995**, 2557.
5. a) Hudlicky, M., *Org. React.*, **1986**, *35*, 513. b) Lafargue, P.; Dodi, A.; Ponchant, M.; Garcia, C.; Lecavorsin, M.; Pujol, J. F.; Lellouche, J. P., *Bioorg. & Med. Chem.* **1994**, *2*, 827. c) Burrell, G.; Evans, J. M.; Jones, G. E. and Stemp, G., *Tetrahedron Lett.*, **1990**, *31*, 3649. d) Devi, N.; Threadgill, M. D. and Tendler J. B., *Synth. Common.*,**1988**, *18*, 1545.
6. Wipf, P.; Miller. C. P., *Tetrahedron Lett.*, **1992**, *33*, 6267.
7. a) Galeotti, N.; Montagne, C.; Poncet, J. and Jouin, P., *Tetrahedron Lett.*, **1992**, *33*, 2807. b) Roush, D. M. and Patel, M. M., *Synth. Commun.*, **1985**, *15*, 675.
8. Yokokawa, F.; Hamada, Y.; Shioiri, T., *Synlett.* **1992**, 153.
9. Vorbruggen, H.; Krolikiewicz, K., *Tetrahedron*, **1993**, *49*, 9353.
10. We have attempted several different methods to hydrolyze ethyl 4-acetyl-5-methyl-isoxazole-3-carboxylate to the corresponding acid, but in our hands all failed, the only product is 2-acetyl-3-oxobutanenitrile:



When ethyl 4-[1-(1,3-dioxolanyl)-ethyl]-5-methyl-isoxazole-3-carbonate was subjected to hydrolysis, the mixture slowly transformed to 2-acetyl-3-oxobutanenitrile at room temperature.

11. Hansen J. F.; Kamata K.; Meyers A. I., *J. Heterocyclic. Chem.* **1973,** *10,* 711.

12. Zhou, P.; Blubaum, J. E.; Burns C. T. and Natale, N. R., *Tetrahedron Lett.*. **1997,** 38(40), 7019.

13. Mokennon M. J.; Meyers A. I., *J. Org. Chem.,* **1993**, *58,* 3568.

14. Leahy, J. W., *Encyclopedia of Reagents for Organic Synthesis,* edited by L. A. Paquette, Vol. 7, P5057, John Wiley & Sons ltd. 1995.

15. Natale, N. R.; McKenna, J. I.; Niou, C. - S.; Borth, M. and Hope, H., *J. Org. Chem.,* **1985,** *50,* 5660.

16. Morcuende, A.; Ors, M.; Valverde, S., and Herradon, B., *J. Org. Chem.*, **1996**, *61,* 5264.

17. Cozzi, P. G.; Floriani, C., *Inorg. Chem.,* **1995**, *34*, 2921.

18. Ryan, C.; Kariv-Miller, E., *Tetrahedron,* **1988**, *44*, 6807.

19. Barrow, C. J.; Sun, H. H., *J. Nat. Prod.,* **1994**, *57*, 471.

20. Chadwick, D. J.; McKnight, M. V.; Ngochindo, R., *J. Chem. Soc. Perkin. Trans. 1,* **1982**, 1343.

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