Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 733–737

Tetrahedron Letters

Novel α-amino amidine synthesis via scandium(III) triflate mediated 3CC Ugi condensation reaction☆

Walter Keung,* Farid Bakir, Andrew P. Patron, Dan Rogers, Chad D. Priest and Vincent Darmohusodo

Department of Chemistry, Senomyx, Inc., 11099 North Torrey Pine Road, La Jolla, CA 92037, USA

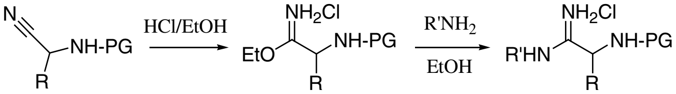
Received 6 October 2003; revised 11 November 2003; accepted 12 November 2003

Abstract—α-Amino amidines are made via a novel scandium(III) triflate catalyzed multi-component reaction involving aldehydes, amines, and isonitrile. The reaction can be automated and is amenable to library production. The chemistry of α-amino amidine described herein can be elaborated further for the synthesis of hydantoin imides and imidopyrazine derivatives.

1. Introduction

In the search for combinatorial methods, which allow for the convenient synthesis of structurally diverse molecules, we focused our efforts toward the preparation of α-amino amidines. α-Amino amidines have found applications in the synthesis of (1) the antitumor antibiotic Bleomycin,[1] (2) iminopeptides,[2,3] (3) intermediates for the study of the bioluminescence of *Cypridina hilgendorfii*,[4] and (4) novacaine derivatives.[5] Unfortunately, the number of publications on α-amino amidine synthesis is limited.[6] Various methods for the synthesis of simple amidines from nitriles have been reported.[7–9] Synthesis of amidines has also been demonstrated utilizing isonitrile.[10] α-Amino amidines have been described by Mengelberg using *N*-protected α-amino iminoethers as intermediates, which are a direct extension of the nitrile method (Scheme 1).[11–13] Recently, Katrisky has observed α-aminoamidines (B) during the purification of the imidoylbenzotriazole intermediate (A) (Scheme 2).[14] Norton has also demonstrated that zirconocene η^2-imine complex can insert carbodiimides which, after protic cleavage, produce α-amino amidines (Scheme 3).[15]

The described methods have not provided a robust method suitable for the production of compound libraries. Work by MacFarland did, however, provide for an interesting Ugi variant, which could be amenable to automated synthesis. In the optimization of the synthesis of *N*-cyclohexyl-α-dimethylaminoisovaleramide, McFarland allowed dimethylamine, isobutyraldehyde, and cyclohexyl isocyanide to react under various conditions to maximize the formation of the α-aminoamide (**D**), a three-component condensation product (Scheme 4). It was demonstrated that α-amino amidine (**C**) was



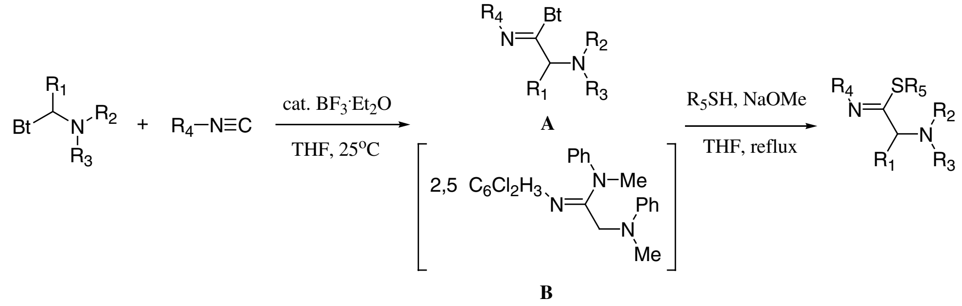
Scheme 1. α-Amino amidines from iminoethers.

Keywords: Aminoamidines; Hydantoin imides; Imidopyrazines; Lanthanides; Multi-component Ugi.

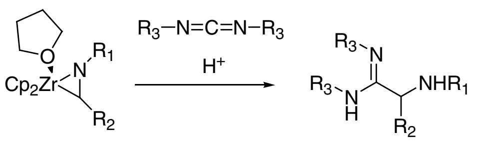
☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.11.051

* Corresponding author. Tel.: +1-858-646-8364; fax: +1-858-404-0752; e-mail: walter.keung@senomyx.com

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.051



Scheme 2. α-Amino amidine formation from α-amino iminothioether synthesis.

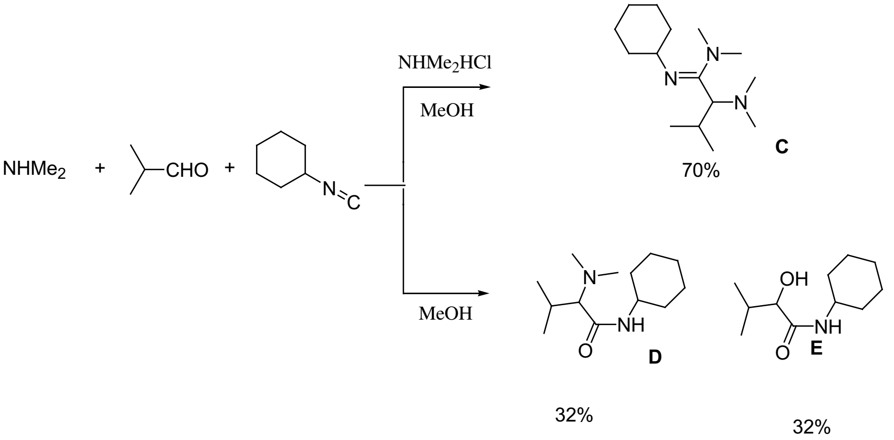


Scheme 3. α-Amino amidine synthesis from carbodiimide.

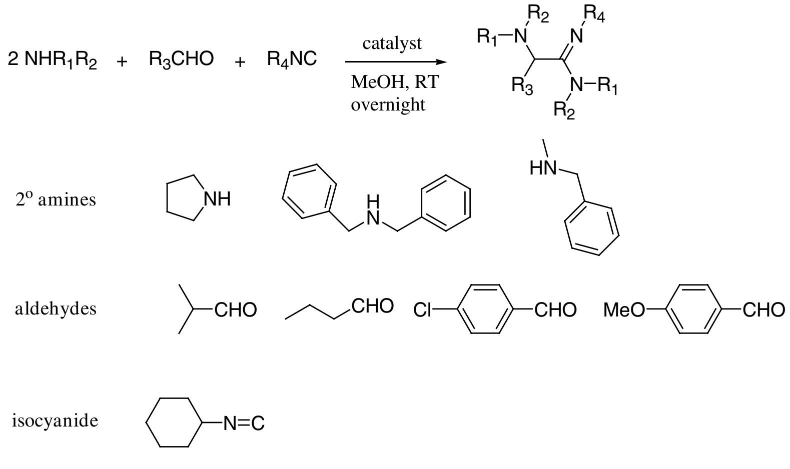
the only product isolated using 1 equiv of dimethylamine hydrochloride as a catalyst.[16] We were intrigued by this result and believed we could optimize the formation of the α-amino amidine.

2. Results and discussion

Previous investigations by McFarland had shown that α-amino amidines could be obtained in 70% yield with a 1:1:1:1 ratio of isobutyraldehyde/cyclohexyl isonitrile/dimethylamine/dimethylamine hydrochloride (Scheme 4).[16] Our initial investigations hoped to elaborate on this Ugi variant, which has received little attention and to optimize the reaction for a high throughput synthesis platform. We initially screened various catalysts on a 12 reaction matrix using the inputs shown in Scheme 5. HCl was included in the study as a reference. A series of



Scheme 4. Ugi variants observed by McFarland.



Scheme 5. Twelve reaction matrix for optimization study.

Table 1. Catalyst screen

Catalyst	Average yield (%)[a]	Average purity (%)[a]
Lanthanum triflate	86	84
Silver triflate	7	12
Yttrium triflate	86	83
Ytterbium triflate	92	83
Copper triflate	20	36
Indium triflate	89	80
Scandium triflate	99	79
Triethylsilyl chloride	55	70
Trimethylsilyl chloride	57	72
Trifluoroacetic acid	69	83
Zinc chloride	59	78
Hydrochloric acid	60	75
p-Tolylsulfonic acid (PTSA)	59	64

[a] Yields and purities were determined byLC/MS ELSD quantification.[17]

Lewis acids was selected based on relative Lewis acidity, stability, and ease of handling.

All reactions were performed on a 20 µmol scale using a Tecan Genesis Workstation 200 liquid handler. The reagents were diluted at 500 mM in methanol and added in the order aldehyde, amine, isonitrile, and catalyst. Lewis acids were screened at 0.25 equivalence (5 µmol) in 500 mM methanol while Brønsted acids were added at 1.0 equivalence (20 µmol) (Table 1). The reactions were performed in a 1.2 mL 96-well Greiner plate. The reactions were sealed and allowed to shake overnight at room temperature.

Scandium(III) triflate demonstrated the highest reactivity of the catalysts screened. Resin bound acids were attempted but did not result in a significant amount of desired product. Although other lanthanum(III) triflates showed good reactivity, scandium triflate was chosen for further optimization based on yield and purity. Further optimization of the catalyst loading was optimal at 0.2 equivalence.

A representative set of amino amidines was synthesized and isolated to establish the scope of this reaction (Table 2). The reactions were performed on a 250 µmol scale at room temperature and were nearly complete after a few hours. The compounds were typically allowed to shake overnight. Methanol was removed under reduced pressure and purified by preparative thin layer chromatography using a 94:5:1 dichloromethane/methanol/triethylamine solvent system.

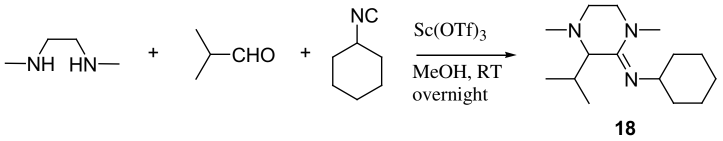
The reactivity is acceptable for most aldehydes. Benzaldehydes give slightly lower yields than aliphatic aldehydes (1,2 vs 3,4). Various amines reacted including amino esters, which produce the corresponding α-amino amidine in 63% yield (13). Anilines produced good yields in this reaction and gave the resulting amino amidine in good to excellent yields 75–98% (14–16). Primary amines such as benzylamine also yielded the corresponding α-amino amidine in 70% yield (17).

The ^{1}H NMR spectra of the α-amino amidines are generally broad with poorly defined peaks and made interpretation difficult. The fluxional behavior of the α-amino amidines has been previously observed by Katritzky in the synthesis of analogous α-amino-*N*-substituted thioacetimidates.[12] The broadness of the peaks was rationalized as a result of slow rotation around C=N bond.

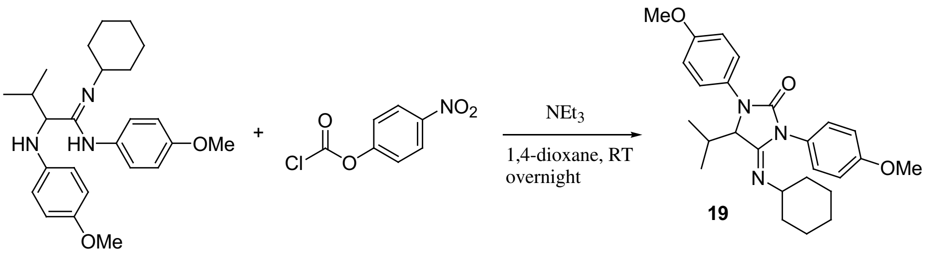
The chemistry was expanded to using diamine. *N*,*N*′-dimethylethylenediamine was used to produce the corresponding imidopyrazine derivative in 70% yield (Scheme 6). It was also necessary to use 0.5 equivalence for the diamine reaction for optimal yield of the imidopyrazine.

The products resulting from the aniline combinations were further elaborated by reacting with *p*-nitrochloroformate to the corresponding hydantoin imide in unoptimized yield of 57% (Scheme 7).

In summary, we have demonstrated the optimization of a Lewis acid catalyzed multi-component α-amino amidine synthesis and its application to automated synthesis. The reaction does not require rigorous anhydrous

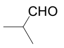
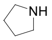
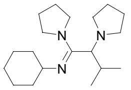
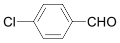
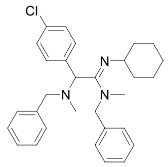
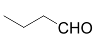
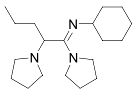
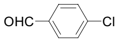
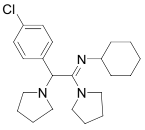
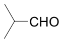
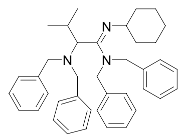
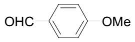
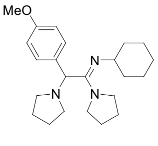
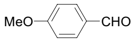
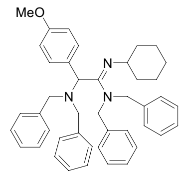
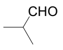
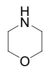
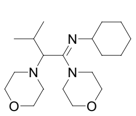
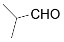
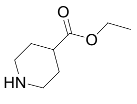
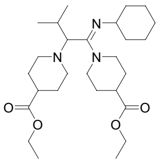
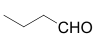
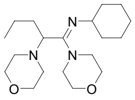
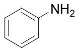
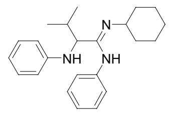
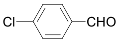
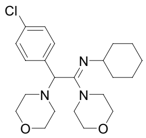
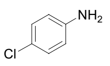
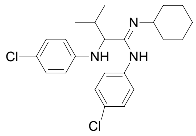
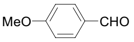
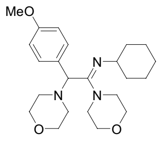
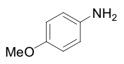
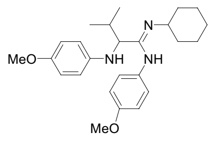
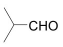
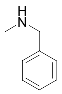
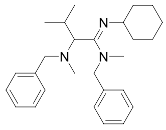
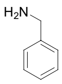
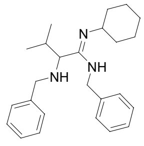


Scheme 6. α-Amino amidine reaction with diamine.



Scheme 7. Formation of hydantoin imide.

Table 2. Selected examples with isolated yields

Entry	Aldehyde	Amine	α-Amino amidine	Yield (%)	Entry	Aldehyde	Amine	α-Amino amidine	Yield (%)
1				90	10		—		77
2		—		73					
3		—		46	11		HNBn$_2$		70
4		—		51	12		—		56
5				89	13				63
6		—		76	14	—			75
7		—		70	15	—			98
8		—		61	16	—			83
9				67	17	—			70

reaction conditions. We have also demonstrated new routes to imidopyrazine and hydantoin imide.

Acknowledgements

The authors acknowledge the contribution of Dr. Hanghui Lui and Miss Marcie Shapiro for providing analytical support.

References and notes

1. Umezuma, H.; Takita, T.; Sugiura, Y.; Otsuka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron* **1984**, *40*, 501–509.
2. Yamada, T.; Suegane, K.; Kuwata, S.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1088–1093.
3. Yamada, T.; Suegane, K.; Miyazawa, S.; Kuwata, S.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 878–883.

4. Goto, T.; Isobe, M.; Coviello, D. A.; Kishi, Y. *Tetrahedron* **1973**, *29*, 2035–2039.
5. Kaufmann, H. P.; Budwig, J.; Mohnke, K. *Chem. Ber.* **1942**, *75*, 1585.
6. (a) Patai, S. *The Chemistry of Amidines and Imidates*; John Wiley and Sons: New York, 1975; Patai, S. In *The Chemistry of Amidines and Imidates*; John Wiley and Sons: New York, 1991; Vol. 2; (b) Barluenga, J.; Aznar, F.; Liz, R. *J. Chem. Soc., Chem. Commun.* **1981**, 1181; (c) Korshin, E. E.; Soboleva, G. I.; Levin, Y. A.; Podval'nyi, E. A.; Efremov, Y. Y. *Zh. Org. Khim.* **1993**, *29*, 577–587; (d) Ueda, T.; Okamoto, Y.; Tsuji, T.; Muraoka, M. *Chem. Pharm. Bull.* **1968**, *26*, 2355–2361.
7. Pinner, A. *Die Iminoather und ihre Derivate*; R. Oppenheim: Berlin, 1892.
8. Garigipati, R. S. *Tetrahedron Lett.* **1990**, *31*, 1969–1972.
9. Moss, R. A.; Ma, W.; Merrer, D. C.; Xue, S. *Tetrahedron Lett.* **1995**, *36*, 8761–8764.
10. Hegarty, A. F.; Chandler, A. *Tetrahedron Lett.* **1980**, *21*, 885–888.
11. Mengelberg, M. *Chem. Ber.* **1956**, *89*, 1185.
12. Yamada, T.; Suegane, K.; Kuwata, S.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1088–1093.
13. Yamada, T.; Suegane, K.; Miyazawa, S.; Kuwata, S.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 878–883.
14. Katritzky, A. R.; Button, M. A.; Busont, S. *J. Org. Chem.* **2001**, *66*, 2865–2868.
15. Norton, J. R.; Tunge, J. A.; Czerwinski, C. J.; Gately, D. A. *Organometallics* **2001**, *20*, 254–260.
16. McFarland, J. W. *J. Org. Chem.* **1963**, *28*, 2179–2181.
17. Kassel, D. B.; Cai, Z.; Xu, R.; Isbell, J. *J. Comb. Chem.* **2002**, *4*, 600–611.