ed out with NaCl. The ether layer which was dried over anhydrous magnesium sulfate, showed a 94% yield of 1-benzylpiperdine by GC analysis.

Acknowledgement. This work was supported by the Organic Chemistry Research Center sponsored by the Korea Science and Engineering Foundation.

References

1. L. I. Zakharkin and I. M. Khorlina, *Tetrahedron Lett.*, 619 (1962).
2. S. H. Kim, J. H. Kim, and N. M. Yoon, *Bull. Korean Chem. Soc.*, **10**, 117 (1989).
3. P. M. Weissman and H. C. Brown, *J. Org. Chem.*, **31**, 283 (1966).
4. (a) M. Muraki and T. Mukaiyama, *Chem. Lett.*, 215 (1975); (b) T. D. Hubert, D. P. Eyman, and D. F. Wiemer, *J. Org. Chem.*, **49**, 2279 (1984).
5. J. S. Cha and S. S. Kwon, *J. Org. Chem.*, **52**, 5487 (1987).: *ibid.*, **55**, 1692 (1990).
6. N. M. Yoon, K. H. Jeong, and D. K. An, *Bull. Korean Chem. Soc.*, **12**, 7 (1991).
7. J. M. Khamma, V. M. Dixit, and N. Anand, *Synthesis* 607 (1975).

Table 1. Reaction of *N,N*-Dimethylhexanamide and *N,N*-Dimethylbenzamide with Sodium Diethyldihydroaluminate (SDDA)[a]

tertiary amide	temp ℃	hydride /comp.[b]	time h	yield, %[c] aldehyde	alcohol	amine	amide
N,N-dimethyl hexanamide	0	1.5	1.0	77	8	0	15
			3.0	79	9	0	11
	0	2	0.5	82	12	0	6
			1.0	85	13	0	2
	0	5	1.0	63	30	7	0
			3.0	58	29	13	0
	25	2	0.5	90	10	0	0
	reflux	5	1.0	10	16	70	0
			3.0	0	12	85	0
N,N-dimethyl benzamide	0	1.5	1.0	88	2	0	8
			3.0	92	3	0	4
	0	2	0.5	92	6	0	0
			1.0	95	4	0	0
	0	5	1.0	71	20	4	0
			3.0	68	28	4	0
	25	2	0.5	92	5	0	0
	reflux	5	1.0	13	27	60	0
			3.0	0	22	78	0

[a] Reactions were carried out by adding one mmol of SDDA in 0.5 m*l* toluene to one mmol of amide in 1.5 m*l* THF (0.5 M in compound). [b] Mole of hydride per mole of compound. [c] Yields were estimated by GLPC.

A New Aldehyde Synthesis from Tertiary Carboxamides with Sodium Diethyldihydroaluminate

Nung Min Yoon* and Young Soo Gyoung†

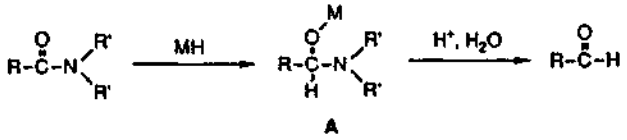
Department of Chemistry, Sogang University, Seoul 121-742
†*Department of Chemistry, Kangreung National University, Kangreung 210-702*

Received May 5, 1992

Reduction of tertiary carboxamides to the corresponding aldehydes is one of the most important and highly desirable means in organic synthesis and numerous methods have been reported, among which reduction with lithium aluminum hydride[1] has been sucessful for 1-acylcarbazole[2], 1-acyl-3,5-dimethylpyrazoles[3], 1-acylimidazoles[4], 1-acylaziridines[5] and *N*-ethylanilides[6]. Partial reduction of *N,N*-dimethylcarboxamides with sodium aluminum hydride[7], lithium di- or triethoxylaluminum hydride[8] and aminoaluminum hydride[9] was also reported to be a useful method for preparation of aldehydes.

Recently we have studied the reducing characteristics of sodium diethyldihydroaluminate (SDDA) systematically, and found that SDDA is a promising selective reducing agent[10]. Thus even with excess SDDA (5 equiv. of hydride), *N,N*-dimethylhexanamide and *N,N*-dimethylbenzamide gave 63% and 71% yields of the corresponding aldehydes respectively in 1 h at 0℃. However with excess hydride at 65℃, the major reduction products were corresponding amines. As shown in Table 1, these dimethylamides were conveniently reduced to the corresponding aldehydes in excellent yields in 0.5-1.0 h at room temperature using equimolar SDDA (2 equiv. of hydride). Therefore, in order to test the generality of this aldehyde synthesis, twenty three representative tertiary amides and two secondary amides were reduced at 25℃ for shorter period of time (usually 0.5-1.0 h) with limited amount of SDDA. The results are summarized in Table 2.

As shwon in Table 2, *N,N*-dimethylamides of less hindered aliphatic acids such as hexanoic acid and isovaleric acid or equally less hindered amides such as 1-hexanoyl pyrrolidine and 1-hexanoyl piperidine were readily reduced to the corresponding aldehydes in 83-90% yields, however, *N,N*-dimethylamides of hindered acids such as cyclohexanecarboxylic



acid and pivalic acid gave only fairly good yields (74% and 63%), and *N,N*-diethylhexanamide and *N,N*-diisopropylhexanamide gave poor yields of aldehyde (46% and 35%). Apparently the tetrahedral intermediate [**A**] is destabilized as R and R' groups become bulkier. The reaction of these bulky amides was slower at our standard conditions (25℃, H/co-

Table 2. Synthesis of Aldehydes by the Partial Reduction of Tertiary Amides with Sodium Diethyldihydroaluminate (SDDA) at 25℃[a]

tertiary amide	hydride /comp.[b]	time h	aldehyde %[c]
N,N-dimethylhexanamide	2	0.5	90
N,N-dimethylisovaleramide	2	1.0	83
N,N-dimethylphenylacetamide	2	1.0	89, 82[d]
N,N-dimethylcyclohexanecarboxamide	2	1.0	74
N,N-dimethylpivalamide	2	1.0	63[d]
1-hexanoylpyrrolidine	2	3.0	95, (80)
1-hexanoylpiperidine	2	3.0	93
N,N-diethylhexanamide	3	1.0	46
N,N-diisopropylhexanamide	4	3.0	35
N,N-dimethylcinnamamide	2	1.0	34[e]
N,N-dimethylbenzamide	2	1.0	92
1-benzoylpyrrolidine	2	1.0	92
1-benzoylpiperidine	2	1.0	93
N-benzoylmorpholine	2	0.5	94
N,N-dimethyl-4-methylbenzamide	2	0.5	94
N-(4-methylbenzoyl)pyrroridine	2	1.0	96
N-(4-methylbenzoyl)piperidine	2	1.0	95
N,N-dimethyl-4-methoxybenzamide	2	0.5	88
N-(4-methoxybenzoyl)pyrrolidine	2	1.0	92, (85)
N-(4-methoxybenzoyl)piperidine	2	1.0	97
N,N-dimethyl-4-chlorobenzamide	2	1.0	87[d]
N,N-dimethyl-4-nitrobenzamide	2	1.0	(92)
N,N-dimethyl-2-naphthylamide	2	1.0	(87)
N-methylhexanamide	4	24	no reaction
N-methylbenzamide	4	24	no reaction

[a]The reaction was carried out by adding one mmol of SDDA in 0.5 m*l* toluene to one mmol of tertiary amide solution in 1.5 m*l* THF (0.5 M in compound). [b]Mole of hydride per mole of compound. [c]Yields were estimated by GLPC; figures in parenthesis are isolated yields (10 mmol scale). [d]Determined as the 2,4-dinitrophenyihydrazone. [e]Reactions at 0℃.

mpd.=2). Thus the reduction of *N,N*-diisopropylhexanamide was incomplete even ater 3 h at 25℃ using 4 equiv of hydride. *N,N*-Dimethylcinnamide, an α,β-unsaturated caboxamide was also tested, but gave only poor yield of aldehyde (34%). This is very similar to lithium di- and triethyoxyaluminohydride which could reduce tetiary amides to the corresponding aldehydes in 70-90% yields, but gave only 7-9% of cinnamaldehyde from *N,N*-dimethylcinnamamide[8].

On the other hand, aromatic tetiary amides were readily reduced to give excellent yields of aldehyde. Even bulky diisopropylbenzamide gave 82% yield of benzaldehyde although the reduction was carried out for 3 h at 25℃ using 4 equiv of hydride. Electron donating methyl and methoxy substituents and electron attracting chloro and nitro substituents did not interfere this aldehyde synthesis. Since nitrobenzene is reduced rapidly with SDDA even at 0℃[10], it is surprising that 4-nitrobenzaldehyde is obtained in 92% yield from *N,N*-dimethyl-4-nitrobenzamide. Finally we examined two representative secondary amides, *N*-methylhexanamide and *N*-methylbenzamide. Both amides evolved hydrogen rapidly but no reduction was observed. This suggests that the selective reduction of tertiary amides could be carried out in the presence of secondary amides.

In conclusion, SDDA is an excellent reagent for the aldehyde synthesis from less hindered aliphatic tertiary amides and aromatic tertiary amides, such as *N,N*-dimethylcarboxamides and *N*-acylpiperdines, since the yield is very good, and the reduction can be carried out at room temperature, for shorter period of time.

Experimental

Materials. SDDA (OMH-1)[11] was purchased from Aldrich Chemical Co. as a 25% solution in toluene and standardized by hydrolyzing a known aliquot of the solution with *t*-BuOH-THF (1 : 1) mixture and measuring the hydrogen evolved. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl and stored under dry nitrogen atmosphere. Most of the organic compounds utilized in this study were the commercial products of the highest purity. They were further purified by distillation or recrystallization when necessary. Tertiary amides were prepared by the method of Brown and Tsukamoto[8]. All glassware was dried thoroughly in a dry nitrogen atmosphere. Hypodermic syringes were used to transfer solution.

Partial Reduction of Tertiary Amides to Aldehydes with SDDA. The reduction of *N,N*-dimethylbenzamide is representative. An oven dried flask fitted with a septum inlet and magnetic stirring bar, and connected to a mercury bubbler was charged with 1.5 m*l* of *N,N*-dimethylbenzamide (1 mmol) solution in THF (*n*-dodecane was added as an internal standard). To this was added 0.5 m*l* of SDDA (1.0 mmol) solution in toluene at 25℃. After 1.0 h reaction, the reaction mixture was hydrolyzed by the addition of water. The organic layer was separated and dried with anhydrous potassium carbonate. The GLPC analysis using 5% Carbowax 20 M column, showed 92% benzaldehyde and 5% benzyl alcohol.

Preparative Reduction of Tertiary Amides to Aldehydes. The following preparative procedure for the reduction of *N,N*-dimethyl-4-nitrobenzamide to the 4-nitrobenzaldehyde is representative. To the flask, typically equipped as above, 1.94 g of *N,N*-dimethyl-4-nitrobenzamide (10 mmol) in 15 m*l* of THF was introduced, and 5 m*l* of SDDA (10 mmol) solution was added over 3 min at 25℃. After 1.0 h reaction, the mixture was decomposed with water and 30 m*l* of ether was added. The ethereal layer was separated, and the aqueous portion extracted with ether (3×10 m*l*), and the combined ethereal extract was dried over $MgSO_4$. The solvents were evaporated *in vacuo* yielding 1.48 g of 4-nitrobenzaldehyde mp. 103-105℃. The aldehyde was recrystallized from hexane-ether to give 1.38 g (92%) of *p*-nitrobenzaldehyde mp. 104-106℃ (lit[12]. mp. 106℃).

Acknowledgment. This work was supported by the Organic Chemistry Research Center sponsored by the Korea Science and Engineering Foundation.

References

1. M. Hudicky, *Reductions in Organic Chemistry*, Ellis Horwood Limited, Chichester, England, 1984.

2. G. Wittig and F. Hornberger, *Ann.*, **577**, 11 (1952).
3. W. Ried and F. J. Konigstein, *Angew. Chem.*, **70**, 165 (1958).
4. H. A. Staab and H. Braunling, *Ann.*, **654**, 119 (1962).
5. H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **83**, 4549 (1961).
6. F. Weygand and G. Eberhardt, *Angew. Chem.*, **64**, 458 (1952).
7. L. I. Zakharkin, D. N. Maslin, and V. V. Gavrilenko, *Tetrahedron*, **25**, 5555 (1969).
8. H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **86**, 1089 (1964).
9. M. Muraki and T. Mukaiyama, *Chem. Lett.*, 875 (1975).
10. A systematic study on the reducing characteristics of sodium diethyldihydroaluminate (SDDA) has been completed, N. M. Yoon, Y. S. Shon, and J. H. Ahn, *Bull. Korean Chem. Soc.*, **13**, 199 (1992).
11. OMH-1 is a commercial name of SDDA.
12. *Handbook of Chemistry and Physics*, 70th ed., CRC press, Boca, Raton, *Florida* U.S.A., 1989.

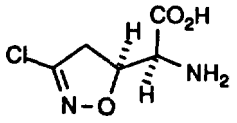
Syntheses of Heterocyclic Amino Acid Derivatives *via* Nitrile Oxide Cycloadditions with β,γ-Unsaturated-α-Amino Acid Compounds

Gyochang Keum, Yong Jun Chung, and Byeang Hyean Kim*

Department of Chemistry, Center for Biofunctional Molecules, Pohang Institute of Science and Technology, P.O.Box 125, Pohang 790-600

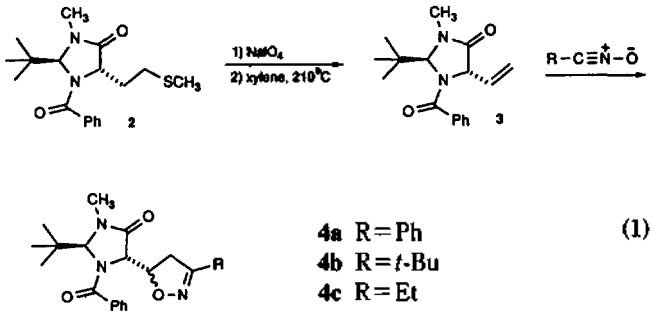
Received February 10, 1992

A novel antitumor antibiotic, (α*S*, 5*S*)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (**1**, AT-125, Acivicin), isolated from fermentation broths of *Streptomyces sviceus*[1], displayed significant activity against a number of tumors in experimental animals[2]. The biological activity of this unusal amino acid and its novel structure have elicited our interest in the synthesis of the related amino acid derivatives possessing 2-isoxazoline rings. We report here the preliminary results of our synthetic efforts.



1 : AT-125(Acivicin)

To synthesize our desired products by cycloadditive approach, we needed to prepare the β,γ-unsaturated-α-amino acid derivatives as chial dipolarophiles. The β,γ-unsaturated-α-amino acids are a class of compounds that possess antibiotic and enzyme inhibitory activity[3]. (2*S*, 5*S*)-Imidazolidinone **2**[4] was prepared from L-methionine in 5 steps (42% overall yield) by a modification of the Seebach's method[5]. Oxidation of **2** by $NaIO_4$ (96%), followed by thermal elimlination of the resulting sulfoxide (88%) provided the desired β,γ-unsaturated-α-amino acid derivative **3**. Dipolar cycloadditions of various nitrile oxides (R=Ph, *t*-Bu, Et) with **3** afforded the corresponding cycloadducts **4a-c** (Eq. 1).

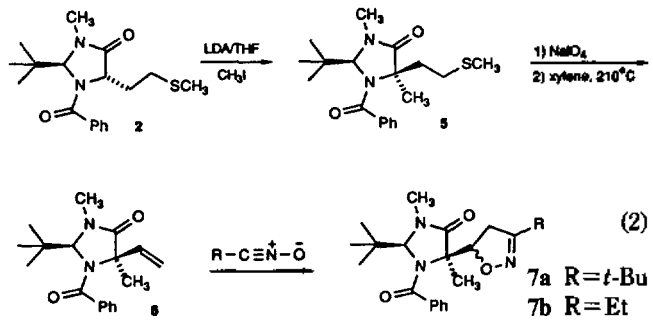


4a R=Ph
4b R=*t*-Bu
4c R=Et (1)

In the case of benzonitrile oxide cycloaddition, a mixture of two diastereomers was obtained. The major diastereomer (**4am**) and minor one of the above cycloaddition were isolated in 56% and 2% yield, respectively. The major cycloadducts of 2,2-dimethylpropionitrile oxide and propionitrile oxide were isolated in 63% and 50% yield, respectively.

These amino acid derivatives possessing 2-isoxazoline rings underwent the pyramidal nitrogen inversion[6]. This dynamic equilibrium was detected by recording ^{1}H-NMR spectra of **4am** at room temperature and 70℃. The ^{1}H-NMR spectrum taken at 70℃ showed the coalescence phenomenon due to the rapid equilibrium between two invertomers[7]. The absolute stereochemistry of the newly generated stereogenic center in the major products of **4a-c** was tentatively assigned as *R* by examining molecular models of **3** and **4a-c**.

L-Vinylalanine derivative **6** was prepared from **2** in 3 steps. Stereoselective methylation[8] of **2** provided **5** in 70% yield. Sequential $NaIO_4$ oxidation (95%) and sulfoxide elimination (93%) afforded the chiral dipolarophile **6**. 2,2-Dimethylpropionitrile oxide and propionitrile oxide cycloadditions with **6** gave the diastereomeric mixtures (60 : 40 in both cases) of cycloadducts **7a-b** in 72% and 52% yield, respectively (Eq. 2).



7a R=*t*-Bu
7b R=Et (2)

The heterocyclic amino acid derivatives **4a-c** and **7a-b** have been easily prepared by nitrile oxide cycloadditions and these compounds have some antiviral activity[9]. Thus, the asymmetric cycloadditive approach[10] to β,γ-unsaturated α-amino acids may provide a general entry for biofunctional heterocyclic amino acid derivatives.

Acknowledgement. We are grateful to Korea Research Foundation and KOSEF for financial support.