One-Pot Conversion of α-Ureido and α-Thioureido Esters to Imidazol-2-ones and Imidazole-2-thiones

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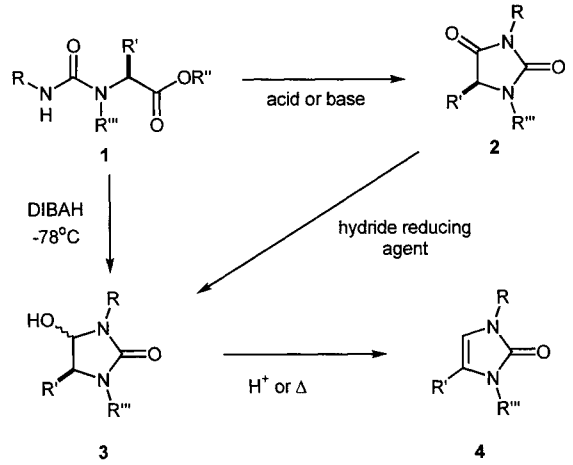
Dedicated to Professor E. J. Corey in honor of his extraordinary contributions to the art of organic synthesis

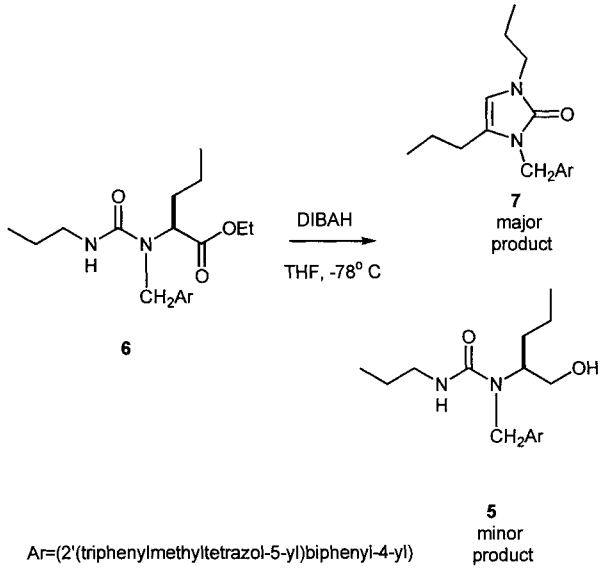
Abstract: 4-Hydroxyimidazolidin-2-ones and 4-hydroxyimidazolidine-2-thiones are obtained by treatment of *N*-(aminocarbonyl)-α-amino esters and *N*-(aminothiocarbonyl)-α-amino esters with diisobutylaluminum hydride (DIBAH). These substances are transformed to imidazol-2-ones and imidazole-2-thiones upon acidic workup.

Cyclic hemiaminals such as **3** are useful building blocks in organic synthesis[1] and as presursors to imidazol-2-ones.[2] This important class of compounds has been synthesized from ureido esters **1** by a two-step sequence (Scheme 1). The esters are first converted to hydantoin derivatives **2**[3] which suffer reduction by various hydride reducing agents[1,4] to give metastable carbinolamine derivatives **3**. Dehydration to **4** occurs under thermal conditions or upon exposure to acid.[4,5]



Scheme 1

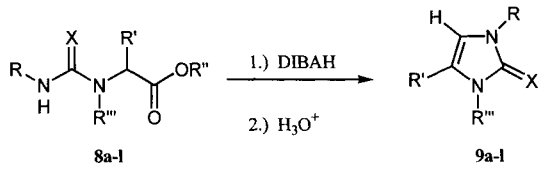
While attempting to synthesize primary alcohol **5** from ester **6** by reduction with an excess of DIBAH it was found that imidazol-2-one **7** was the major product (Scheme 2). This is the first reported example of a one-pot conversion of ureido esters **1** to imidazol-2-ones **4**, and it represents an advance over current methodology for this transformation.[6] When acidic conditions are avoided in the workup the intermediate 4-hydroxyimidazolidinone **3** can be isolated.



Scheme 2

Table I illustrates the scope of this reaction with substituted ureas **8**[7] (X = O) being converted to imidazolones **9**[8] (X = O) The reaction proceeds smoothly with a wide variety of substituents at R and R'. Because the regioselectivity of this transformation is controlled by the connectivity of the starting urea, products are isolated as single regioisomers. When R is an alkyl or benzyl substituent, these reactions are generally quite clean with little overreduction occurring. Substrates having aryl groups at R are susceptible to overreduction, although this effect can be subtle (Table I, entries **c** and **f**). Methylene chloride and ether have been used as solvents in several cases where the starting material is insoluble in toluene.

Table I



8a-l **9a-l**

Entry	R	R'	R''	R'''	X	Method	Yield %
a	CH_2Ph	*n*-Bu	Et	H	O	A	90
b	*i*-Pr	*n*-Bu	Et	H	O	A	90
c	*o*-ClPh	*n*-Bu	Et	H	O	B	64**
d	*t*-Bu	*n*-Pr	Me	H	O	A	80
e	Et	CH_2Ph	Me	H	O	A	93
f	*m*-ClPh	*n*-Pr	Me	H	O	B	---**
g	CH_2Ph	Ph	Me	H	O	C	86
h	*cyc*-Pr	*n*-Bu	Et	H	S	A	75
i	*p*-MeOPh	*i*-Pr	Me	H	S	A	75
j	*n*-Bu	H	Et	Me	S	A	88
k	*n*-Bu	*p*-HObenzyl	Me	H	S	A	72
l	Ph	Me	CH_2Ph	H	S	A	67

*Dehydration method A(see example in ref. 10): The reaction mixture was shaken for 5 min. with 4 M aq. HCl. Method B: The crude hydroxyimidazolidinones were stirred in 97:3 acetone-con. aq. HCl for 1 h. Method C: Reduction was quenched with ethyl acetate, treated with HCl in dioxane, and the aluminum salts dissolved with an aqueous solution of Rochelle salt. The product was isolated by filtration.

**Significant over-reduction occurred in these examples.

---None of the desired material was isolated from this reaction.

Trisubstituted ureas **10**[7] (X = O) are converted under these conditions to 1,3-substituted imidazolones **11**[8] (X = O). The scope of this transformation is illustrated in Table II. These examples are related to the angiotensin II antagonist Cozaar®[9]. Compounds of this type have been shown to function as potent angiotensin II antagonists[6]. The conditions employed for dehydration of the intermediate 4-hydroxyimidazolidinones also served to remove the trityl protecting group present in this series.

Extension of this methodology to thioureidoesters **8h-l**[7] and **10h**[7] (X=S) provides imidazole-2-thiones **9h-l**[8] and **11h**[8,9] (X = S). This new entry into 1,3-disubstituted imidazole-2-thiones is potentially important as they are inaccessable by *N*-alkylation of mono-*N*-substituted imidazole-2-thiones.

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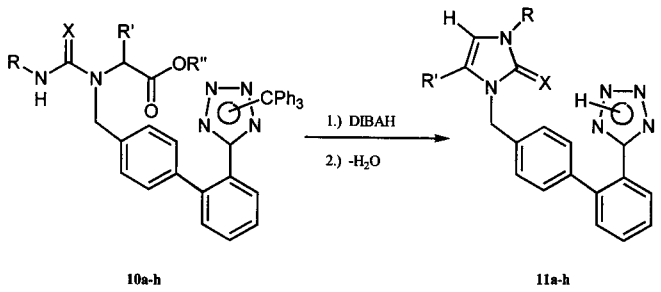
Table II



10a-h 11a-h

Entry	R	R'	R''	X	Method	Yield %
a	Et	*n*-Pr	Et	O	B	72
b	*n*-Pr	*n*-Pr	Et	O	A	75
c	Ph	*n*-Pr	Et	O	B	39**
d	CH_2CF_3	*n*-Pr	Et	O	B	23**
e	*i*-Pr	*i*-Bu	Et	O	B	74
f	Et	allyl	Et	O	D	39
g	*cyc*-Pr	*n*-Pr	Me	O	B	69
h	*n*-Pr	*n*-Pr	Et	S	B	82

*Dehydration method A(see example in ref. 10): The reaction mixture was shaken for 5 min. with 4 M aq. HCl. Method B: The crude hydroxyimidazolidinones (or -thiones) were stirred in 97:3 acetone-con. aq. HCl for 1 h. Method D: The crude hydroxyimidazolidinones were stirred at reflux in MeOH for 22 h.

**Significant overreduction occurred in these examples

In summary, a new synthesis of imidazol-2-ones and imidazole-2-thiones by the reductive cyclization of ureido- and thioureido esters is presented. This methodology is of value because of its generality and ready availability of the starting materials

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References and Notes

(1) Corey, E. J.; Mehrotra, M. M. *Tetrahedron Lett.* **1988**, *29*, 57; Cortes, S.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2246.

(2) For other routes to imidazolones and imidazolthiones see: McCombie, H.; Scarborough, H. *J. Chem. Soc.* **1913**, *103*, 56; Doney, J. J.; Altland, H. W. *J. Heterocyclic Chem.* **1979**, *16*, 1057; Anschutz, R.; Schwickerath, K. *Ann.* **1894**, *284*, 9; Aoyama, H.; Sakamoto, M.; Ohnota, M.; Omote, Y. *Chem. Lett.* **1983**, 1905; Divanfard, H. R.; Ibrahim, Y. A.; Joullié, M. M. *J. Heterocyclic Chem.* **1978**, *15*, 691.

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(4) Red-Al®: Li, C.; Lee, M. H.; Sartorelli, A. C. *J. Med. Chem.* **1979**, *22*, 1030; $NaBH_4$/HOAc: Robertson, A. D.; Martin, G. R.; Buckingham, J. S. European Patent Application EP 0313397 A1, 29 April 1989; $LiAlH_4$: Cortes, S.; Kohy, H. *J. Org. Chem.* **1983**, *48*, 2246.

(5) Otter, B. A.; Falco, E. A.; Fox, J. J. *J. Org. Chem.* **1969**, *34*, 2636.

(6) The preparation of an imidazol-2-one by $LiAlH_4$ reduction of the *N*-butyl ureide of norleucine *N*-methyl-*N*-methoxy amide has been reported: Reitz, D. B.; Manning, R. E. U. S. Patent 5,087,634. 11 February 1992.

(7) Ureido esters and thioureido esters were prepared from the chloroformamide derivative $ClCON(CH_2Ar)CHR'CO_2R''$ of the appropriate α-amino ester.

(8) All imidazolone and imidazolethione products gave IR, ^1H NMR, and HRMS or combustion data consistent with the proposed structures.

(9) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525.

(10) A typical procedure is as follows: To a stirred, cooled (-78°C) solution of 1.01 g (4.00 mmol) of ester **8e** in 30 mL of 1:1 toluene-CH_2Cl_2 was added 3.3 mL (5.0 mmol) of a 1.5 M solution of DIBAH in toluene. The solution was stirred at -78°C for 30 min, and the cold bath was removed. After 5 min., 4 mL of ethyl acetate was introduced, followed by 25 mL of ether and 50 mL of a half-saturated aqueous potassium sodium tartrate solution. The mixture was stirred for 1h, separated, and the aqueous phase was extracted with 10 mL of $CHCl_3$. The combined organic extracts were vigorously shaken for 5 min with 4 M aqueous HCl. The organic phase was then dried ($MgSO_4$) and concentrated under reduced pressure to afford 753 mg (93%) of imidazol-2-one **9e** as a pale yellow oil. ^1H NMR (300 MHz) ($CDCl_3$): δ 9.59(br. s, 1H, NH), 7.21-7.38(m, 5H, aromatic), 5.77(s, 1H, imidazolone H5); 3.69(s, 2H, $C\underline{H}_2Ph$), 3.58(q, 2H, J = 7.3 Hz, NCH_2), 1.23(t, 3H, J = 7.3 Hz, CH_3). High Resolution Mass Spectrum: M/Z Calc. for $C_{12}H_{15}N_2O$ $(M + H)^+$, 203.1180; Found, 203.1184. In many cases no purification is required as the product obtained is greater than 95% homogeneous.

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