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A Convenient Reduction of Substituted Amino-acid Esters

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Abstract : Esters having N-alkyl-N-acyl (or thioacyl) functionality at the α-position are smoothly reduced with $NaBH_4$-MeOH at 0-5°C in very good yields.

It is well-known that sodium borohydride, a frequently used reducing agent, is unable to reduce esters except those containing an α-hydroxy (or oxo) substituent or carrying an electron withdrawing group in the alcohol moiety, or when the reaction is carried out in refluxing t-butanol containing methanol[1]. We therefore used the reagent (in acetic acid at 10°C) to reduce the enamine double bond of the 2-oxopyrroline **1a**. To our utter surprise, the carbomethoxy group was also reduced simultaneously. In fact, carrying out the reduction in methanol at 0-5°C showed that while the ester group reacted almost instantaneously, the double bond remained unaffected under the conditions[2].

We therefore investigated the reactivity of several other substituted esters (**1b-e, 3a-c, 5a, 5b, 6a, 6c, 7, 8** and methyl pivalate)[3] to realize the scope of this unusual reduction. The results presented in Table 1 show that facile reduction took place in most cases with high yields. The products (**2a-e, 4a, 4b, 5c, 6b, 6d** and **9**) were characterized mainly from spectral data. The ester carbonyl stretching band around 1740 cm^{-1} was missing in the IR spectra of the reduction products. In the ^1H NMR spectra the 3H singlet around δ3.7 was replaced by a 2H multiplet around δ3.4 and the C-CH_3 singlet showed appreciable (0.2-0.4 ppm) upfield shift. Appropriate molecular ions were observed in the mass spectra of representative compounds.

It is apparent from the results that though the reduction is not limited to tertiary esters, the presence of an N-alkyl-N-acyl (or thioacyl) functionality at the α-position is essential. Thus **3c** or the methyl esters of pivalic acid, proline (**5a**) or N-benzoylalanine (**7**) were all recovered unchanged after the usual reaction period while **5b** and **8** underwent smooth conversion. Also, the reaction was somewhat sluggish with an N-thioacyl derivative (*viz.* **3a** vs **3b**). As expected, the free carbonyl group in **6a** was reduced during the course of the reaction along with the ester functionality.

As regards the reaction conditions it was noted that the reduction did not occur in aprotic solvents like ether, diglyme or DMSO after prolonged standing at room temperature or, in case of diglyme, heating over steam bath for 2 hr. On addition of a small amount of methanol however, reaction was observed to take place in such media, albeit slowly (smoothly in DMSO). Reduction also occured in ethylene glycol or acetic acid in absence of methanol. It appears therefore that an alkoxy (or an acyloxy) borohydride is the reducing species, assisted by the electron withdrawing capacity of the N-acyl substituent (anion formation in α-NHCOR substituent perhaps hinders its electron withdrawing capacity).

The results provide a very convenient procedure for the reduction of appropriately substituted amino-acid esters. Besides, the vulnerability of such functionalities to sodium borohydride needs to be borne in mind by investigators involved in the chemistry of amino-acids.

Table 1 - Results of $NaBH_4$ reduction[a,b]

Substrate	**1a**	**1b**	**1c**	**1d**	**1e**	**3a**	**3b**	**5b**	**6a**	**6c**	**8**
(Mp, °C)						(130-132)	(150)	(83-84)	(205-206)	(178-179)	(gum)
Product	**2a**	**2b**	**2c**	**2d**	**2e**	**4a**	**4b**	**5c**	**6b**	**6d**	**9**
(Mp, °C)	(180-182)	(210-212)	(205-206)	(>270)	(gum)	(121-122)	(160-162)	(gum)	(138-140)	(169-170)	(gum)
Yield (%)	96	93	92	90	89	97	95	93	91	98	74

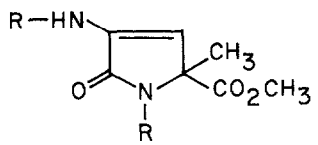
[a] Compound **3c**, obtained as gum, did not react; so also methyl esters of pivalic acid, proline (**5a**) and N-benzoylalanine (**7**).

[b] All the new compounds gave satisfactory elemental analyses.

Typical procedure - Conversion of 1a to 2a : Sodium borohydride (330 mg, 10 mmol) was added portionwise to a solution of **1a** (644 mg, 2 mmol) in methanol (5 ml) at 0-5°C and stirred for 15 min. Water (10 ml) was added and the mixture extracted with dichloromethane (3x15 ml). The dichloromethane extract was dried (Na_2SO_4) and evaporated. The crude product (**2a**) was recrystallised from chloroform-pet. ether; yield 553 mg (96%).

Preparation of **3a, 3b, 3c** and **6a**

Compound **6a** was obtained from **1a** by hydrolysis with conc. HCl (yield 50%), **3a** (72%) by ketalization of **6a** with ethylene glycol/p-TSA in benzene, **3b** (65%) from **3a** by



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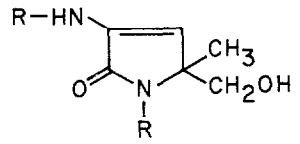
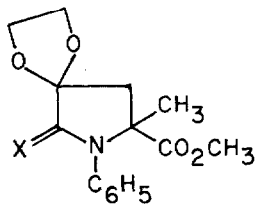


2

a) R = C_6H_5 ; b) R = 4−Cl−C_6H_4 ; c) R = 4−CH_3−C_6H_4 ;
d) R = 4−CH_3CONH−C_6H_4 ; e) R = $C_6H_5CH_2$



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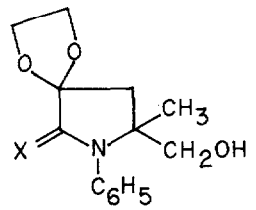

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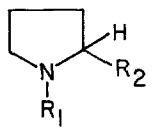
a) X = O ; b) X = S ; c) X = H_2



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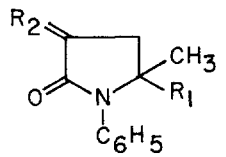
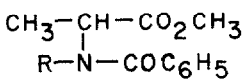


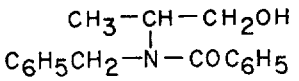
6

a) R_1 = H , R_2 = CO_2CH_3
b) R_1 = COC_6H_5 , R_2 = CO_2CH_3
c) R_1 = COC_6H_5 , R_2 = CH_2OH

a) R_1 = CO_2CH_3 ; R_2 = O
b) R_1 = CH_2OH ; R_2 = H , OH
c) R_1 = CO_2CH_3 ; R_2 = H , NHC_6H_5
d) R_1 = CH_2OH ; R_2 = H , NHC_6H_5



7 R = H
8 R = $CH_2C_6H_5$



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thiolation (Lawesson's reagent) and **3c** (91%) by desulphurization of **3b** with Raney Ni.

Preparation of **5b**

*Benzoylation of proline methyl ester (**5a**) afforded **5b** (63%).*

Preparation of **8**

Compound **8** was prepared from alanine methyl ester **7** by $NaBH_4$ reduction of its benzaldehyde imine followed by benzoylation (yield 58%).

Acknowledgement

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REFERENCE AND NOTES

1. Soai, K.; Oyamada, H.; Ookawa, A. Synth. Commun. **1982,** 12, 463-467.
2. The reverse selectivity i.e., saturation of the double bond in **1a** without affecting the ester group could, on the other hand, be achieved quantitatively using $NaCNBH_3$ in acetic acid, IR spectrum of the product **6c** lacked the 1645 cm^{-1} absorption band while the 1H singlet at δ6.3 was absent in the ^1H NMR spectra.
3. Compounds **1a-e** were synthesized by ultrasound irradiation of the mixture of *methylpyruvate and the respective amines in dichloromethane*[4].
4. Mandal, S. B. ; Achari, B. Indian J. Chem. (Communicated).

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