Tetrahedron Letters, Vol.31, No.26, pp 3739-3742, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

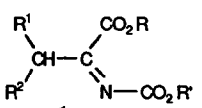
SYNTHESIS AND REACTIVITY OF PROTECTED β-BROMO α-IMINOACIDS ; A CONVENIENT ROUTE TO STRUCTURALLY DIVERSIFIED AMINOACIDS.

R. Danion-Bougot, D. Danion* and G. Francis.

Groupe de Recherches de Physicochimie structurale, associé au C.N.R.S., Université de Rennes I, 35042 Rennes, France.

Abstract - The title compounds are obtained by N-bromosuccinimide oxidation of protected didehydroaminoacids. Additions to the imino group are readily performed with borohydride, Grignard reagents or other nucleophiles. Heterocyclic aminoacids are available by subsequent displacement of bromine.

Structurally diversified α-aminoacids are of considerable interest due to their potential biological activity, as enzyme inhibitors for instance [1]. Different routes to these compounds have been investigated, based on the use of synthetic equivalents of electrophilic or nucleophilic aminoacids synthons. Iminoacids **1** [2] or metalated Schiff bases **2** [3] are representative examples.



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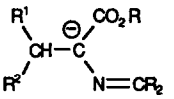

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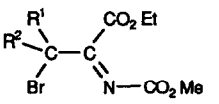
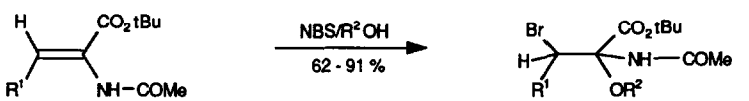


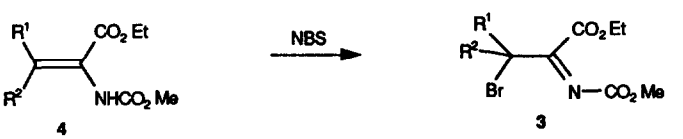
3

We now report the synthesis and our initial investigations of the reactivity of β-bromo α-iminoacid derivatives **3**, as biselectrophilic synthetic intermediates.

In an earlier report, the synthesis of β-bromo α-alkoxyaminoacids was achieved by N-bromosuccinimide oxidation of didehydroaminoacids in the appropriate alcohol [4].

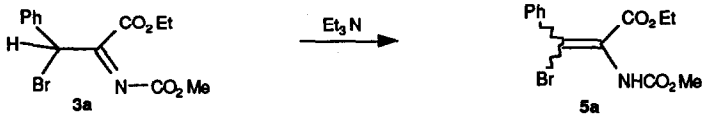


The choice of methylene chloride as a non nucleophilic solvent allowed us to isolate the intermediate β-bromo α-iminoacid derivatives **3**. Protected didehydroaminoacids **4a** (R^1 = Ph, R^2 = H) and **4b** (R^1 = R^2 = Me), obtained according to Schmidt [5], are reacted with an equimolecular amount of NBS in methylene chloride, at room temperature during 12 hrs. Brominated imines **3** are obtained by dissolution in hot pentane, and filtration of the resulting succinimide. They are pure enough [6] for further use.



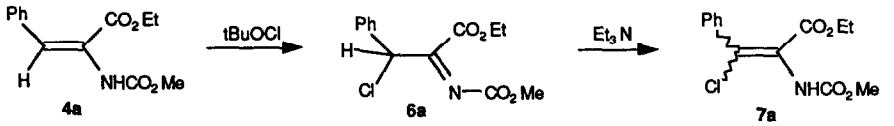
4 **3**

Compound **3a** can be converted to the stable β-bromoenamine **5a** [7] by triethylamine.



3a **5a**

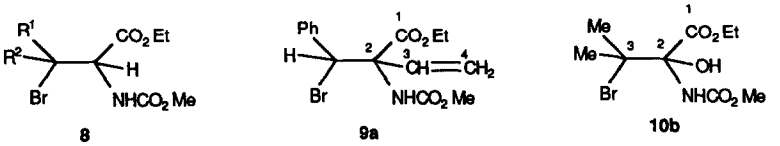
NCS gives no reaction with didehydroaminoacids **4**. To prepare β-chloroiminoacids **6**, we had to use t-butyl hypochlorite as a chlorinating agent. β-chloroenamine **7a** [9] results from **6a** [8] by reaction with Et_3N.



4a **6a** **7a**

The reaction between **3** and common nucleophiles was investigated in order to state precisely the usefulness of these synthetic intermediates, as shown below :

Sodium borohydride. The reaction, performed at 0°C in ethanol with an equimolecular amount of the reagent, is quantitative after 5 min., affording protected β-bromoaminoacids **8** [10]. **8a** is obtained as a cristalline mixture of two diastereoisomers (A/B = 65/35) which are isolated by crystallization (unknown configuration).

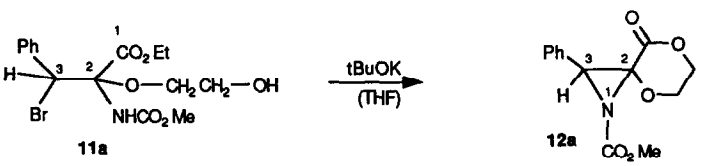


8 **9a** **10b**

Vinylmagnesium bromide. Two molar equivalents of the Grignard reagent in THF are added at -80°C to the bromoimine **3a**. The reaction is then quenched at room temperature and the mixture of diastereoisomers **9a** (A/B = 75/25) is separated by thin layer chromatography [11].

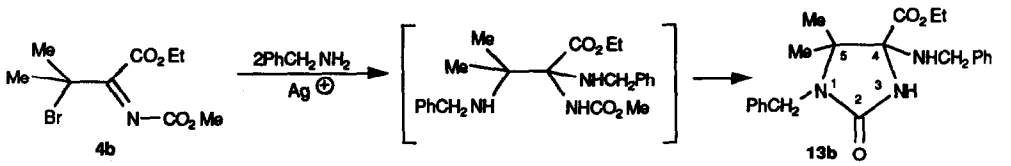
Oxygene nucleophiles. Compounds **3** are sensitive to moisture, and add water. With acid catalysis in aqueous media, the hydrate **10b** formation is instantaneous [12].

Ethylene glycol in excess gives an analogous reaction. α-alkoxyaminoacid **11a** [13], on treatment with potassium tert-butoxide, is converted to the spiroaziridine **12a** [14].

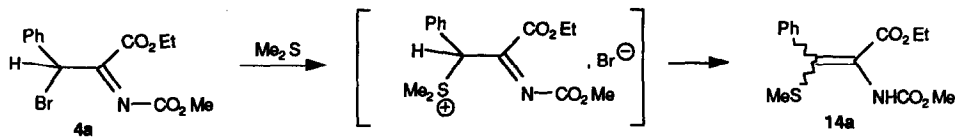


11a **12a**

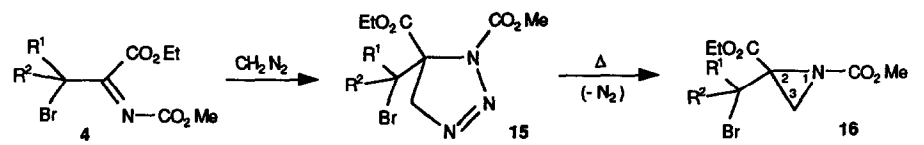
Nitrogen nucleophiles; With benzylamine, an excess of the reagent, in the presence of silver salts, is used to avoid the formation of mixtures. The obtention of the cyclic urea **13b** [15] is interpreted as the result of consecutive α-addition and β-substitution.



Sulfur nucleophiles. Dimethylsulfide provides a convenient access to β-methylthiodidehydroaminoacids. The most probable route to **14a** [16] is the formation of a sulfonium salt, followed by isomerization and conversion to the sulfide by nucleophilic attack, a serious side reaction during the alkylation of dimethylsulfide [17].



The reactivity of the imino function is also exemplified by 1,3-dipolar cycloaddition with diazomethane. Triazolines **15** [18], obtained in almost quantitative yield, are converted, in boiling toluene, into the stable brominated aziridines **16** [19]. Such reactions between diazomethane and acceptor-substituted imines are known to occur readily [20].



This preliminary work clearly shows the interest of intermediates **3** as precursors of β-halo or vinylic aminoacids, related to common enzyme inhibitors [1]. Heterocyclic aminoacids are also readily available by nucleophilic addition to the imine moiety and bromine substitution.

Mechanism and stereochemistry studies of these reactions are under further investigation.

References and notes

1 - M.J. Jung, "Chemistry and Biochemistry of the Aminoacids", G.C. Barret Ed., Chapman and Hall, London, New York, Ch. 7 (1985).

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6 - All isolated compounds gave satisfactory elemental analysis (An.) or mass spectra (MS). Spectral data are in full agreement with the proposed structures and only selected data are cited. IR spectra refer to nujol suspensions (νcm^{-1}) and NMR spectra to $CDCl_3$ solutions (δ ppm ; J Hz) ; ^{13}C spectra were recorded at 20.115 MHz or 75.462 MHz and ^1H spectra at 80 MHz, unless otherwise specified.

3a oil ; 95 % yield. ^1H NMR δ : 6.12 (s, R^2 = H) ; 4.25 (q, OCH_2) ; 3.82 (s, OCH_3) ; 1.25 (t, CH_3). **3b** oil ; 98 % yield. ^1H NMR δ : 4.33 (q, OCH_2) ; 3.83 (s, OCH_3) ; 2.04 (s, R^1= R^2 = CH_3) ; 1.32 (t,CH_3).

7 - **5a** mp 91° ; 87 % yield ; An.. IR ν : 3270 (NH) ; 1720 and 1690 (C=O) ; 1620 (C=C). ^{1}H NMR δ : 6.67 (s, NH) ; 3.96 (q, OCH_2) ; 3.72 (s, OCH_3) ; 0.87 (t, CH_3).

8 - **6a** oil ; quantitative yield. ^{1}H NMR δ : 6.04 (s, CH) ; 4.20 (q, OCH_2) ; 3.83 (s, OCH_3) ; 1.20 (t, CH_3).

9 - **7a**, two isomers (**A/B** = 65/35). **7aA** mp 76° ; 61 % yield ; An.. IR ν : 3275 (NH) ; 1720 and 1690 (C=O) ; 1625 (C=C). ^{1}H NMR δ : 6.68 (s, NH) ; 4.00 (q, OCH_2) ; 3.76 (s, OCH_3) ; 0.94 (t, CH_3). **7aB** mp 76° ; 36 % yield ; An.. IR ν : 3280 (NH) ; 1720 and 1690 (C=O) ; 1620 (C=C). ^{1}H NMR δ : 6.24 (s, NH) ; 4.35 (q, OCH_2) ; 3.63 (s, OCH_3) ; 1.36 (t, CH_3).

10 - **8a**, two diastereoisomers (**A/B** = 65/35) **8aA** mp 76° ; 60 % yield ; An.. IR ν : 3330 (NH) ; 1730 and 1690 (C=O). ^{1}H NMR (300 MHz) δ : 5.56 (d, J = 9,7, NH) ; 5.51 (d, J = 3,9, R^2 = H) ; 4.85 (dd, J = 9.7 and 3.9, CHNH ; irradiation at 4.85 gives singlets at 5.56 and 5.51). **8aB** mp 76° ; 20 % yield ; An.. IR ν : 3310 (NH) ; 1725 and 1680 (C=O). ^{1}H NMR (300 MHz) δ : 5.33 (d, J = 9,0, NH) ; 5.33 (d, J = 6.0, R^2 = H) ; 4.98 (dd, J = 9.0 and 6.0, CHNH ; irradiation at 4.98 gives a singlet at 5.33). **8b** oil ; 80 % yield ; MS. IR ν : 3360 (NH) ; 1720 (broad, C=O). ^{1}H NMR δ : 5.79 (d, J = 9.2, NH) ; 4.37 (d, J = 9.2, CHNH).

11 - **9a**, two diastereoisomers (**A/B** = 75/25) **9aA** mp 74° ; 50 % yield ; An.. IR ν : 3420 (NH) ; 1725 (C=O); 1635 (C=C). ^{1}H NMR δ : 5.87 (s, NH) ; 5.48 (s, CHBr) ; ABX syst. : 5.36 (A) and 5.29 (B), H^4 ; 6.20 (X), H^3 ; J_{AB} = 1.1, J_{AX} = 10.9, J_{BX} = 16.9. **9aB** mp 74° ; 15 % yield ; MS. IR ν : 3420 (NH) ; 1730 (C=O) ; 1635 (C=C). ^{1}H NMR δ : 5.37 (broad s, NH) ; 5.46 (s, CHBr) ; ABX syst. : 5.30 (A) and 5.11 (B), H^4 ; 6.30 (X), H^3 ; J_{AB} = 0, J_{AX} = 10.4, J_{BX} = 17.6. ^{13}C NMR δ : 132.1 (d, ^1J = 164, C^3) ; 117.8 (dd, ^1J = 157 et 160, C^4) ; 68.1 (s, C^2) ; 59.4 (d, ^1J = 155, CHBr).

12 - **10b** mp 44° ; 83 % yield ; MS. IR ν : 3360 (broad ; NH, OH) ; 1730 (C=O). ^{1}H NMR δ : 6.00 (s, NH) ; 4.90 (s, OH). ^{13}C NMR δ : 86.2 (s, C^2) ; 67.8 (s, C^3).

13 - **11a** mp 95° ; 88 % yield ; An.. IR ν : 3600 to 3100 (OH) with 3530, 3410 and 3210 (NH) ; 1745 and 1720 (C=O). ^{1}H NMR δ : 5.41 (s, NH and CHBr) ; 3.89 to 3.40 (m, OCH_2CH_2O) ; 2.33 (s, OH). ^{13}C NMR δ : 87.7 (s, C^2) ; 66.6 (t, ^1J = 145) and 61.8 (t, ^1J = 143) (OCH_2CH_2O) ; 54.9 (d, ^1J = 155, C^3).

14 - **12a** mp 118° ; 74 % yield ; An.. IR ν : 1745 and 1675 (C=O). ^{1}H NMR δ : 4.28 (s, H^3) ; 4.62 to 3.85 (m, OCH_2CH_2O). ^{13}C NMR δ : 163.2 (s, cyclic C=O) ; 72.3 (broad s, C^2) ; 68.8 (t, ^1J = 151) and 62.8 (t, ^1J = 148) (OCH_2CH_2O) ; 51.0 (d, ^1J = 173, C^3).

15 - **13b** mp 104°, 64 % yield ; An.. IR ν : 3230 (broad, NH) ; 1740 and 1690 (C=O). ^{1}H NMR δ : 5.93 (s) and 2.37 (broad s) (2 NH) ; 4.49 and 4.15 (J_{AB} = 16) and 3.81 and 3.54 (J_{AB} = 13) (2 $PhCH_2$). ^{13}C NMR δ : 159.4 (broad s, C^2) ; 80.4 (broad s, C^4) ; 64.9 (broad s, C^5) ; 47.2 (t, ^1J = 134) and 42.8 (t, ^1J = 136) (2$PhCH_2$).

16 - **14a** mp 111°, 62 % yield ; MS. IR ν : 3280 (NH) ; 1715 and 1695 (C=O). ^{1}H NMR δ : 6.55 (s, NH) ; 1.84 (s, SCH_3).

17 - B.M. Trost and L. Melvin, "Sulfur Ylids", Academic Press, New York, London, p. 6 (1975).

18 - **15a**, two diastereisomers (**A/B** = 50/50), oil. ^{1}H NMR δ : 6.22 (s) and 5.85 (s) (2CHBr) ; 2 AB syst. : 5.46 and 4.87 ; J_{AB} = 19 and 5.16 and 4.92 ; J_{AB} = 17 (2 cyclic CH_2). **15b** mp 80° (dec) ; 76 % yield ; An.. IR ν : 1735 (broad, C=O) 1550 (N=N). ^{1}H NMR δ : 5.09 and 4.83 ; J_{AB} = 19 (cyclic CH_2).

19 - **16a**, two diastereoisomers (**A/B** = 50/50). **16aA** mp 74° ; 20 % yield ; An.. IR ν : 1755 and 1745 (C=O). ^{1}H NMR δ : 5.65 (s, CHBr) ; 2.75 (d, J = 1.5) and 1.96 (d, J = 1.5) (cyclic CH_2). ^{13}C NMR δ : 49.6 (d, ^1J = 153, CHBr) ; 48.5 (s, C^2) ; 37.8 (dd, ^1J = 181 and 189, C^3). **16aB** ^{1}H NMR δ : 5.70 (s, CHBr) ; 2.85 (d, J = 1) and 2.65 (d, J = 1) (cyclic CH_2). **16b** oil ; 87 % yield; An.. IR ν : 1735 (broad, C=O) ; ^{1}H NMR δ : 2.90 (d, J = 1) and 2.59 (d, J = 1) (cyclic CH_2). ^{13}C NMR δ : 60.9 (s, C^2) ; 51.0 (s, CBr) ; 36.4 (dd, ^1J = 174 and 180, C^3).

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(Received in France 23 March 1990)