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REACTION OF SCHIFF BASES ANIONS WITH 4-HALO-2-BUTENOATES : SELECTIVE SYNTHESIS OF α-CYCLOPROPYL AND γ,δ UNSATURATED α-AMINO ACID DERIVATIVES.

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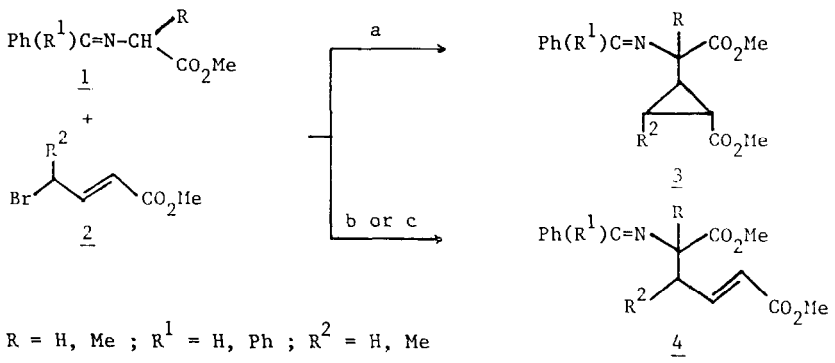
Depending on the reaction conditions, anions of imines derived from α-aminoesters react with 4-bromo - 2-butenoates to give either cyclopropyl derivatives by an addition-elimination or γ,δ-unsaturated imino-esters by a nucleophilic substitution.

In a previous paper we have described the formation of 1-aza (2·1·0)-bicyclopentanes from the addition reactions of imine anions to methyl 2-bromoacrylates[1]. We now report the behaviour of such imine anions 1 with 4-bromo - 2-butenoates 2.

When the reaction was performed at -78° with LDA in THF, 1 and 2 reacted to give rise to cyclopropanes 3 in good yields. Addition of HMPA to the mixture gave specific substitution products leading to γ,δ-unsaturated imino derivatives 4 as it was observed under PTC condition reactions[2].



R = H, Me ; R^1 = H, Ph ; R^2 = H, Me

a = LDA, THF, -78°, 10 mn

b = LDA, THF, HMPA, -78° to RT, overnight

c = $|PhCH_2N(C_2H_5)_3|^+HSO_4^-$, 10 % NaOH, CH_2Cl_2

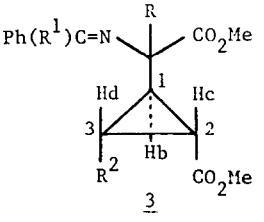
Cyclopropane ring formation by anionic Michael addition reactions to alkenes such as 2 was previously reported[3] and applied mainly in the area of pyrethroïds[4]

To our knowledge, the reaction of imine anions with alkenes 2 has not been described and represents an easy and direct way for α-cyclopropyl α-aminoacids synthesis.

Thus, equimolecular amounts of LDA and 1a (R = H ; R^1 = Ph) in THF reacted quantitatively with 2a (R^2 = H) after 10 min. at -78°C. Hydrolysis at low temperature followed by usual work-up led to 3a (R = R^2 = H ; R^1 = Ph), (F = 90°C, Ether-Hexane ; yields : 85 %).

3a ^{1}H-NMR (Bruker AM 300 WB) : 7.10-7.70 (10H ; Ph) ; 3.87 d (1H, Ha, J_{ab} = 6.1 Hz) ; 3.72 and 3.67 s (6H, CO_2Me) ; 2.09 m (1H, Hb, J_{ab} = 6.1 Hz ; J_{bc} = 6.3 Hz (trans) ; J_{cd} = 4.2 Hz (tr.) $J_{bd'}$ = 8.7 Hz (cis)) ; 1.76 m (1H, Hd, J_{bd} = 4.2 Hz (tr.) ; J_{cd} = 8.4 Hz (tr.) ; $J_{dd'}$ = 5 Hz) ; 1.19 m (1H, Hd', $J_{bd'}$ = 8.7 Hz (tr.) ; $J_{cd'}$ = 4.4 Hz (tr.) ; $J_{dd'}$ = 5 Hz) ; 0.87 m (1H, Hc, J_{bc} = 6.3 Hz (tr.) ; J_{cd} = 8.4 Hz (c) ; $J_{cd'}$ = 4.4 Hz (tr.)).
Mass spectrometry (Varian MAT 311) : m/e = 351, $M^{+\cdot}$: $C_{21}H_{21}NO_4$ (calculated 351.1471 ; found 351.1482).

The following compounds were obtained :



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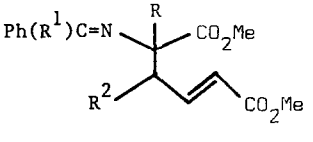
3a. R = Ha, R^1 = Ph, R^2 = Hd' ; (mp = 90°C, Ether/Hexane, 85 %).
3b. R = Ha, R^1 = H, R^2 = Hd' ; ($Bp_{0.03}$ = 170°C, 67 %).
3c. R = Me, R^1 = H, R^2 = Hd' ; ($Bp_{0.03}$ = 195°C, 70 %).
3d. R = Ha, R^1 = Ph, R^1 = Me ; (mp = 87°C, Ether/Hexane, 78 %).
3e. R = R^2 = Me, R^1 = H ; ($Bp_{0.025}$ = 130°C, 71 %).

Stereochemistry on the cyclopropane ring was assigned from NMR data, based on the coupling constants values ($J_{cis} > J_{trans}$; J_{cis} : 8-10 Hz ; J_{tr} : 4-6 Hz)[5]. *For all these derivatives iminogroup at C_1 and ester group at C_2 are in a trans relationship. Methyl at C_3 is cis related to the ester group at C_2 (3d, 3e).*

When compounds 1 and 2 were reacted with LDA in THF, HMPA (-78°C to rt) for 14 hours or by PTC at room temperature[2,7], γ,δ-unsaturated imino derivatives 4 were recovered in good yields. Spectroscopic data are in good agreement with the proposed structures.



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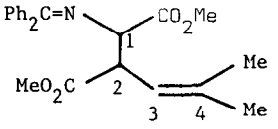

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4a. R = R^2 = H, R^1 = Ph (90 %)
4b. R = Me, R^1 = R^2 = H (88 %)
4c. R = Ph, R^1 = R^2 = H (85 %)
4d. R = H, R^1 = Ph, R^2 = Me (92 %).

^{1}H NMR : 7.05-7.65 (10H, Ph) ; 4.95 dq (1H, H_3, J_{23} = 10 Hz ; $^4J_{3\text{-Me}}$ = 1.4 Hz) ; 4.55 d (1H, H_1, J_{12} = 8 Hz) ; 4.00 dd (1H, H_2, J_{12} = 8 Hz, J_{23} = 10 Hz) ; 3.70 and 3.60 s (6H, CO_2Me) ; 1.68 and 1.72 d (6H, Me, $^4J_{3\text{-Me}}$ = 1.4 Hz).

Methyl 4-bromo-4-methyl-2-pentenoate and anion of imine 1a (R = H, R^1 = Ph) either with LDA, THF, HMPA or with PTC gave rise to the unsaturated compound 5, which resulted formally from SN_2' substitution disfavored in this case by the ester group[8].

We are at this time investigating other aminoacids synthesis by the reaction of iminoester anions with other haloalkenes derivatives.

1. B. Fouchet, M. Joucla and J. Hamelin, Tetrahedron Lett., 1981, 3397.
2. R.D. Allan, J. Chem. Res. (S), 1980, 392, (M), 1980, 4658.
3. P. Kolsaker and H.J. Storesund, J. Chem. Soc. Chem. Comm., 1972, 375.
4. S. Torii, H. Tanaka and Y. Nagai, Bull. Chem. Soc. Jpn, 1977, 50, 2825.
5. A.J. Gordon and R.A. Ford, in "The Chemist's Companion", J. Wiley and Sons, Ed., 1972, p. 274.
6. I. Wagner and H. Musso, Angew. Chem. Internat. Ed., 1983, 22, 816.
7. M.J. O'Donnell, J.M. Boniece and S.E. Earp, Tetrahedron Lett., 1978, 2641.
8. Electrophilic centers were expected at the sp^3 carbon bonded to the halide and at the sp^2 carbon β related to the ester group.

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