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REACTION OF ETHYL 2-AZIDOPROPENOATE WITH NUCLEOPHILES

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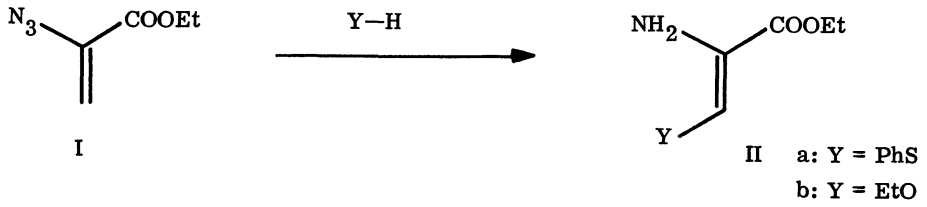
The title compound is transformed into ethyl 2-aminopropenoate having 3-phenylthio or 3-ethoxy substituent upon treatment with thiophenol or sodium (or lithium) ethoxide in ethanol, respectively. The reaction with ethyl mercaptoacetate is also discussed.

As ethyl 2-azidopropenoate (I) is readily accessible by the procedure described in the preceding paper,[1] we have studied its reaction with various nucleophiles and found this process provides us with a facile entry to (Z)-2-aminopropenoates having a hetero-atom substituent at C-3.

Treatment of I (0.141 g, 1.0 mmol) with thiophenol (0.110 g, 1.0 mmol) in ethanol (5 ml) at room temperature for 1.5 h resulted in evolution of nitrogen gas to give ethyl 2-amino-3-phenylthiopropenoate (IIa)[2] in 69-73% yields after work-up and column chromatography. The product was uniform by TLC analysis and gave following spectra. IR (neat): 1710, 1610, 1480, 1240, 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.25 (s); MS: m/e 223 (M^+). Transformation of IIa into the N-chloroacetyl derivative ($ClCH_2COCl$, Et_3N, CH_2Cl_2, 0°C, 1.5 h, r t., 1.5 h) followed by purification by preparative TLC gave ethyl (Z)-2-(chloroacetamido)-3-phenylthiopropenoate[2] [mp 109-110°C, ^1H NMR: δ 7.65 (s)] along with its (E)-isomer [^1H NMR δ 8.13 (s)] in 56% yield in a ratio of 55:1. The stereochemistry of these was determined on the basis of the literature values.[3] Thus, the configuration of IIa was assigned to (Z) of more than 98% purity.

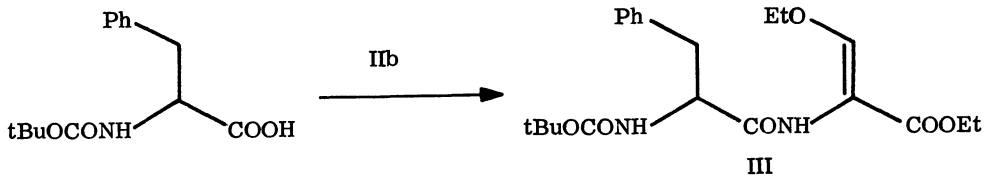
When I was stirred in ethanol containing an equimolar amount of lithium or sodium ethoxide, ethyl 2-amino-3-ethoxypropenoate (IIb)[4] was produced in 63 or 59% yield, respectively, IR: 1710 1580, 1320 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.63 (s). Derivatization of IIb as above gave a single isomer of ethyl 2-chloroacetamido-3-ethoxypropenoate[2] (mp 77-79°C) exhibiting ^1H-NMR absorption ($CDCl_3$) at δ 7.37 (s). In analogy to the stereochemical result of IIa, IIb should have (Z)-configuration. Acetylation of IIb (Ac_2O, pyridine, r.t., overnight) followed by hydrogenation (10% Pd/C, EtOH, H_2, 1 atm) gave ethyl 2-acetamido-3-ethoxypropanoate[5] in 88% overall yield.



I

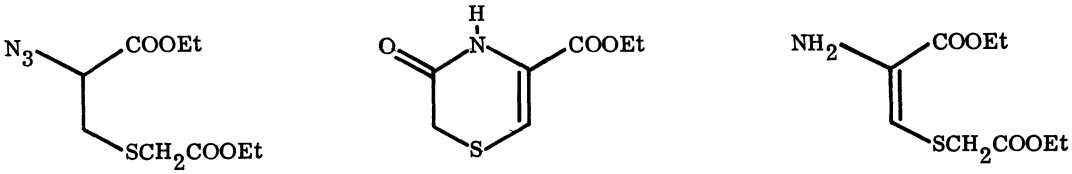
II a: Y = PhS
b: Y = EtO

Condensation of IIb with N-(t-butoxycarbonyl)phenylalanine (dicyclohexylcarbodiimide, r.t., 15 h) gave the dipeptide III[2] (mp 93-95°C) in 89% yield. Thus, IIa and IIb may find their application as unnatural dehydro amino acid components.[6]



III

Upon treatment with an equimolar amount of ethyl mercaptoacetate in ethanol, I was transformed into a Michael adduct IV[2,7] in 84% yield which was treated with lithium ethoxide in ethanol to give V[8] (mp 70-73°C, 59% yield) accompanied by an oil tentatively assigned to VI[9] (14%). VI was not converted into V under the conditions. Decomposition of IV into V and VI was also effected with 1,8-diazabicyclo[5.3.0]undec-7-ene.



IV V VI

It is worthy to note that the conjugate addition of nucleophiles to I is particularly facilitated by the liberation of nitrogen gas to give the adduct under the mild conditions. The products reported herein have potential biological activity. Studies along this line are in progress in our laboratories.

References

1. M. Kakimoto, K. Kai, and K. Kondo, Chem. Lett., 1982, 525.
2. The compound gave correct elemental analysis data. All the crystalline products were recrystallized from hexane-ethyl acetate mixture.
3. C. Shin, M. Hayakawa, T. Sazuki, A. Ohtsuka, and J. Yoshimura, Bull. Chem. Soc. Jpn., 51, 550 (1978). The (E) isomer generally gives an olefinic absorption at 0.3-0.5 ppm lower field than the (Z) isomer.
4. IIb was characterized as a urea derivative, mp 148-150°C (ref 2), which was produced by the reaction with phenylisocyanate.
5. IR: 3300, 1740, 1660, 1530 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.20 and 1.30 (2t, J = 7 Hz, totally 6 H), 2.07 (s, 3H), 3.40 (q, J = 7 Hz, 2H), 3.63 (dd, J = 3, 9 Hz, 1H), 3.83 (dd, J = 3, 9 Hz, 1H), 4.22 (q, J = 7 Hz, 2H) 4.70 (dt, J = 9, 3 Hz, 1H), 6 2-6.5 (br, 1H). Cf. M. Jaeger, S. Iskric, and M. Wickerhauser, Croat. Chem. Acta 28, 5 (1956); Chem. Abstr., 51, 1840a (1957).
6. Y. Shimohigashi and N. Izumiya, J. Synth. Org. Chem. Jpn., 36, 1023 (1978); C. Shin, ibid., 37, 830 (1979).
7. IR: 2120, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 and 1.37 (2t, J = 6 Hz, 6H), 3.0-3.2 (m, 2H), 3.35 (s, 2H), 4.15 and 4.28 (2q, J = 6 Hz, 3H), 3.35 (s, 2H), 4.28 (q, J = 6 Hz, 2H), 6.80 (s, 1H), 8.2-8.6 (br, 1H).
8. ^1H NMR ($CDCl_3$): δ 1.30 (t, J = 6 Hz, 3H), 3.35 (s, 2H), 4.28 (q, J = 6 Hz, 2H), 6.80 (s, 1H), 8.2-8.6 (br, 1H).
9. IR: 3300, 3060, 1720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.1-1.4 (2t, 6H), 3.38 (s, 2H), 3.78 (s, 2H), 4.1-4.4 (2q, 4H), 6.83 (s, 1H).

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