Addition of 6-Azidotetrazolo[1,5-*b*]pyridazine to Acrylates

B. Stanovnik

Department of Chemistry, University of Ljubljana, Ljubljana, Yugoslavia

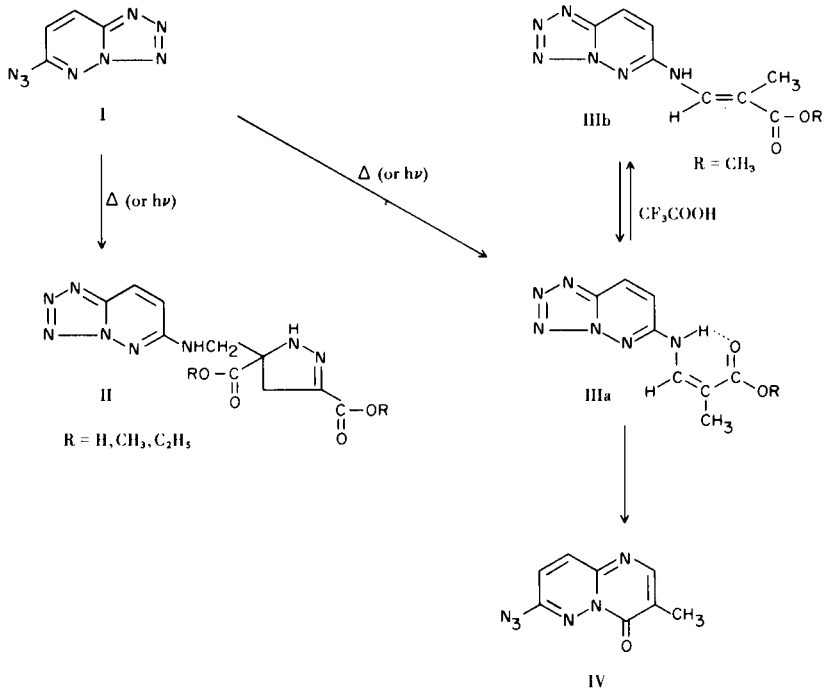
Received July 7, 1971

A paper (1) has appeared recently which describes the reaction between 6-azidotetrazolo[1,5-*b*]pyridazine and dimethyl acetylenedicarboxylate. We now wish to report our observations on addition of 6-azidotetrazolo[1,5-*b*]-pyridazine to methyl or ethyl acrylate and methyl methacrylate.

When 6-azidotetrazolo[1,5-*b*]pyridazine (I) was heated under reflux in methyl or ethyl acrylate a product was isolated in a high yield, which was indicated by the elemental analysis to be a 1:2 adduct. The same compound was isolated when 6-azidotetrazolo[1,5-*b*]pyridazine and methyl or ethyl acrylate in 1:1 molar ratio were heated either in refluxing toluene or left in the dark for several weeks, or irradiated with uv light (350 mμ) at room temperature. The latter reaction was finished in 3 hours giving almost a quantitative yield of II, (R = CH_3 or C_2H_5). Hydrolysis in alkaline solution gave the corresponding dicarboxylic acid (II, R = H).

The structure of the product was established mainly on the basis of ir and nmr spectra. The ir spectrum shows two carbonyl absorption bands at 1720 cm^{-1} and 1750 cm^{-1} typical for a conjugated and an unconjugated ester carbonyl groups, two NH absorption bands at 3350 cm^{-1} and 3300 cm^{-1} which were displaced to 2370 cm^{-1} (broad band) when the compound was treated with deuterium oxide in the presence of traces of hydrochloric acid. The nmr spectrum shows two different ester ethyl groups at τ = 8.68 and 8.73 and τ = 5.85 and 5.95, a singlet corresponding to an isolated -CH_2-group at τ 6.80, an AB pattern at τ = 5.95 and τ = 6.25 with the geminal coupling constant J_{CH_2} = 15 Hz and an AB pattern at τ = 2.79 and τ = 1.72 (J_{78} = 9.4 Hz) corresponding to H_7 and H_8 of the tetrazolo[1,5-*b*]pyridazine residue and a broad band at τ = 8.60 for NH groups.

On the basis of this information one can conclude that the compound is diethyl 5-[6′-tetrazolo[1,5-*b*]pyrida-



zinyl)aminomethyl]-Δ^2-pyrazolin-3,5-dicarboxylate. We believe that the compound is formed according to the mechanism proposed by Huisgen *et al.* (2) for the addition of phenylazide to ethyl acrylate in the presence of triethylamine. In our case neither the triazoline derivative nor diazo ester, the possible intermediates, could be isolated.

On the other hand, (I) and methyl methacrylate under reflux or when irradiated with uv light (350 mμ) at room temperature gave a product (IIIa), the structure of which was established on the basis of nmr and ir spectra to be methyl (*Z*)-β-(6′-tetrazolo[1,5-*b*]pyridazinyl)aminomethacrylate (the "*cis*" isomer).

The nmr spectrum shows that there is only one isomer present in the solution. From ir spectrum (1690 cm^{-1} for ester > CO group, and 3220 cm^{-1} for NH) it is possible to conclude that the "*cis*" isomer is the most probable one. When traces of trifluoroacetic acid were added to the solution, a new quartet for an ethylenic proton appeared at lower field (τ = 1.78) indicating the isomerization of *cis* (IIIa) to *trans* (IIIb) isomer. The *cis* isomer predominates in the equilibrium.

In addition, the compound (IIIa) was transformed into 7-azidopyrimido[1,2-*b*]pyridazin-4-one (IV), involving azidotetrazolo valence isomerization, which we have studied recently on similar heterocyclic systems (3,4,5), showing that the *cis* isomer must be present in acidic solution.

EXPERIMENTAL (6)

Diethyl 5-[(6′-Tetrazolo[1,5-*b*]pyridazinyl)aminomethyl]-Δ^2-pyrazoline-3,5-dicarboxylate (II, R = ethyl).

Method A.

A mixture of 1 g. of I and 5 ml. of ethyl acrylate was heated under reflux for two hours. Upon cooling the precipitate was separated by filtration, washed with ethanol and recrystallized from a mixture (4:1) of ethanol and DMF, yield 72%, m.p. 166°.

Anal. Calcd. for $C_{14}H_{18}N_8O_4$: C, 46.41; H, 5.01; N, 30.93. Found: C, 46.48; H, 5.12; N, 30.76.

Method B.

To a solution of 0.81 g. (0.005 mole) of I in 10 ml. of toluene 0.50 g. (0.005 mole) of ethyl acrylate was added and the mixture was heated under reflux for 3 hours. Ethyl acrylate was evaporated *in vacuo* and the residue recrystallized from a mixture (4:1) of ethanol and DMF giving 0.73 g. (80%) of II (R = ethyl), m.p. 166°. The compound was identical in every respect with the compound prepared by method A).

Method C.

A mixture of 1 g. of I and 10 ml. of ethyl acrylate was left in a stoppered flask at room temperature exposed to daylight. The reaction followed by tlc was completed in 10 days. The compound was isolated as above, giving an almost quantitative yield of II (R = ethyl).

When the same mixture was left in the dark, the reaction, followed by tlc, was completed in two months giving II (R = ethyl) in a quantitative yield.

Method D.

A solution of 200 mg. of I in 20 ml. of ethyl acrylate was placed in a cylindrical quartz tube and irradiated in Rayonet photochemical reactor using 16 RUL-3500 Å lamps. The temperature of the solution was 30° during the irradiation. The reaction was followed by tlc as above. The excess of ethyl acrylate was evaporated *in vacuo*, and the remaining solid recrystallized from a mixture (4:1) of ethanol and DMF, giving II (R = ethyl) in almost quantitative yield.

Dimethyl 5-[(6′-Tetrazolo[1,5-*b*]pyridazinyl)aminomethyl]-Δ^2-pyrazoline-3,5-dicarboxylate (II, R = methyl).

The compound was prepared according to method A from I and methyl acrylate. The product was recrystallized from a mixture (4:1) of ethanol and dimethylformamide, yield 82%, m.p. 190-191°.

Anal. Calcd. for $C_{12}H_{14}N_8O_4$: C, 43.11; H, 4.22; N, 33.55. Found: C, 43.35; H, 4.40; N, 33.49.

5-[(6′-Tetrazolo[1,5-*b*]pyridazinyl)aminomethyl]-Δ^2-pyrazoline-3,5-dicarboxylic Acid (II, R = H).

Hydrolysis of II (R = ethyl).

Compound II (R = ethyl) (250 mg.) was heated with 2 ml. of 5% sodium hydroxide solution under reflux for 30 minutes. After cooling the solution was acidified (*p*H = 3-4) with concentrated hydrochloric acid and left in the refrigerator for two hours. The precipitate was collected and washed with water, yield 50%, m.p. 188-189° after recrystallization from a mixture (4:1) of ethanol and DMF.

Anal. Calcd. for $C_{10}H_{10}N_8O_4$: C, 39.19; H, 3.29; N, 36.59. Found: C, 38.79; H, 3.21; N, 36.35.

Methyl (*Z*)-β-(6′-Tetrazolo[1,5-*b*]pyridazinyl)aminomethacrylate (IIIa) ("*cis*"-Isomer).

Method A.

A mixture of 0.81 g. of I and 5 ml. of methyl methacrylate was heated under reflux for 2 hours. Upon cooling the precipitate was separated by filtration and washed with ethanol, giving 0.9 g. (68%) of IIIa, m.p. 265° after recrystallization from a mixture (4:1) of ethanol and DMF. Nmr spectrum (in DMSO-d_6) τ = 8.15 (=C-C*H*$_3$, d), τ = 2.0 (=C*H*, q), J_{H,CH_3} = 1.5 Hz, τ = 6.3 (COOC*H*$_3$, s), τ = 2.66 (7-H, d), τ = 1.59 (8-H, d), J_{78} = 9 Hz, τ = 6.70 (NH, broad). Mass spectrum: M^+ = 234.

Anal. Calcd. for $C_9H_{10}N_6O_2$: C, 46.15; H, 4.30; N, 35.88. Found: C, 46.29; H, 4.46; N, 35.86.

Method B.

A solution of 50 mg. of I in 10 ml. of methyl methacrylate was irradiated for 5 hours in Rayonet photochemical reactor using 16 8W low pressure RUL-3500 Å lamps. The temperature of the solution during the irradiation was 30°. The excess of methyl methacrylate was evaporated *in vacuo* and the residue recrystallized as above, giving 57% of compound IIIa.

Cis-trans Isomerization.

Compound IIIa (47 mg.) was dissolved in 0.5 ml. of DMSO-d_6 and traces of trifluoroacetic acid added. Immediately a new quartet at lower field arose corresponding to the ethylenic proton for the *trans* isomer (IIIb). The ratio *cis:trans* (60:40) does not change considerably in the temperature range from 25° to 115°. The solution was then diluted with 3 ml. of water, the precipitate collected, washed with water and ethanol and dried *in vacuum*, giving IIIa (*cis* isomer).

7-Azido-3-methyl-pyrimido[1,2-*b*]pyridazin-4-one (IV).

A mixture of 0.94 g. of IIIa and 10 g. of PPA (~ 83% of phosphorus pentoxide) was heated at 100° for 1 hour. The mixture was then cooled on ice, 30 g. of crushed ice was added and the mixture was neutralized with solid sodium bicarbonate. The solution was extracted with chloroform (5 x 30 ml.). The combined extracts were dried with anhydrous sodium sulphate, filtered and evaporated *in vacuo*. The remaining solid was recrystallized from ethanol, yield 0.47 g. (58%) of IV, m.p. 120° dec. Nmr spectrum (in DMSO-d_6) τ = 1.90 (2-H, q), τ = 7.89 (3-CH_3, d), $J_{2H,3\text{-}CH_3}$ = 0.9 Hz, τ = 2.75 (8-H, d), τ = 2.16 (9-H d), $J_{8,9}$ = 9.4 Hz. Mass spectrum: M^+ = 202.

Anal. Calcd. for $C_8H_6N_6O$: C, 47.52; H, 2.99; N, 41.57. Found: C, 47.63; H, 3.38; N, 41.72.

Acknowledgment.

We wish to thank Professor M. Tišler from Department of Chemistry, University of Ljubljana, for discussions and Dr. J. Marsel from Institute J. Stefan, Ljubljana, for recording the mass spectra.

REFERENCES

(1) T. Sasaki, K. Kanematsu, M. Murata, *J. Org. Chem.*, **36**, 446 (1971).

(2) R. Huisgen, G. Szeimies, L. Möbius, *Chem. Ber.*, **99**, 475 (1966).

(3) B. Stanovnik, M. Tišler, *Tetrahedron*, **25**, 3313 (1969).

(4) B. Stanovnik, M. Tišler, M. Ceglar, V. Bah, *J. Org. Chem.*, **35**, 1139 (1970).

(5) B. Stanovnik, M. Tišler, *Synthesis*, 1970, 180.

(6) Melting points were determined on a Kofler micro hot stage and are corrected. Ir spectra were recorded on a Perkin-Elmer 137. Infracord as potassium bromide discs, nmr spectra of solutions in DMSO-d_6 were taken on a JEOL JNM-C-60 HL spectrometer using tetramethyl silane as internal standard, mass spectra were recorded on a CEC 21-110 C instrument using direct sample insertion into the ion source which was operating at 120° and ionization voltage of 70 V.