SYNTHESIS OF 4H-PYRAZOLO[1,5-a][1,3]DIAZEPINE[1]

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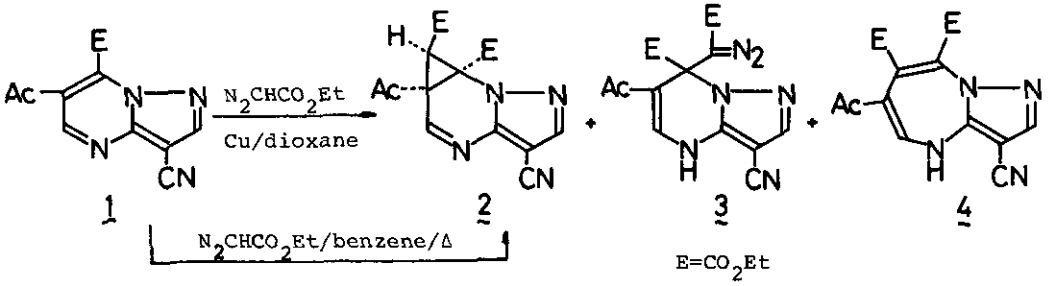
Abstract ——— 6-Acetyl-8-ethoxycarbonyl-4H-pyrazolo[1,5-a][1,3]-diazepine-3-carbonitrile (5) was synthesized by treatment of 2 with silicic acid.

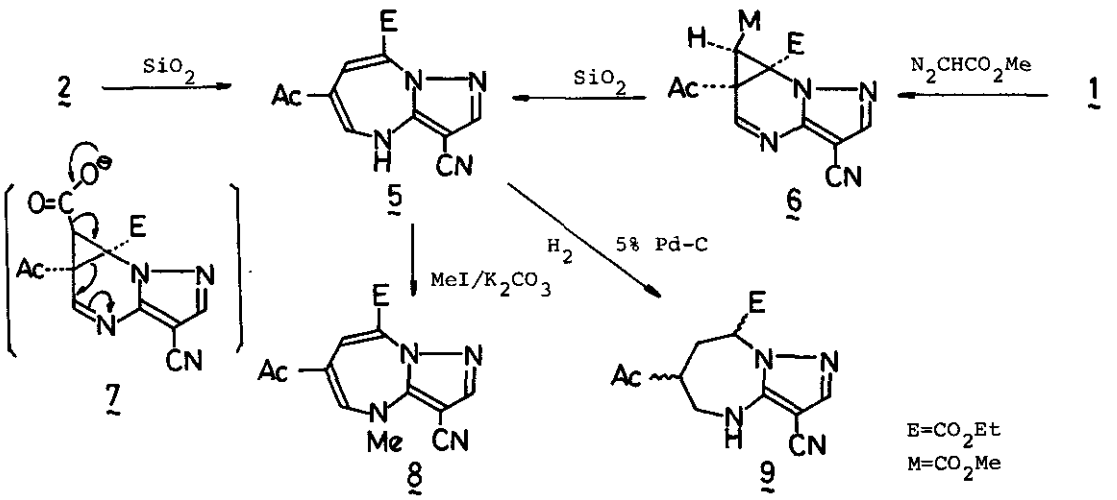
We have reported the ring transformation of 5a-acetyl-6a-ethoxycarbonyl-5a,6a-dihydro-6H-cyclopropa[e]pyrazolo[1,5-a]pyrimidine-3-carbonitrile into other heterocycles via cleavage of cyclopropane ring.[2] Recently, 9H-imidazo[1,2-a][1,3]diazepines were synthesized by ring expansion of 5H-cyclopropa[e]imidazo[1,2-a]-pyrimidine derivative.[3] On the continuation of our further exploring ring transformation of cyclopropapyrimidines, it is important to study the substituent effect on cyclopropane ring. Previously, we reported the reaction of 1 with ethyl diazoacetate in the presence of copper powder in dioxane gave a mixture, from which the cyclopropane derivative (2) (62%) and the diazo compound (3) (2.2%) were obtained by recrystallization from EtOH.[4] We reinvestigated this reaction, because 2 will be an adequate compound to study the substituent effect.



1 2 3 4

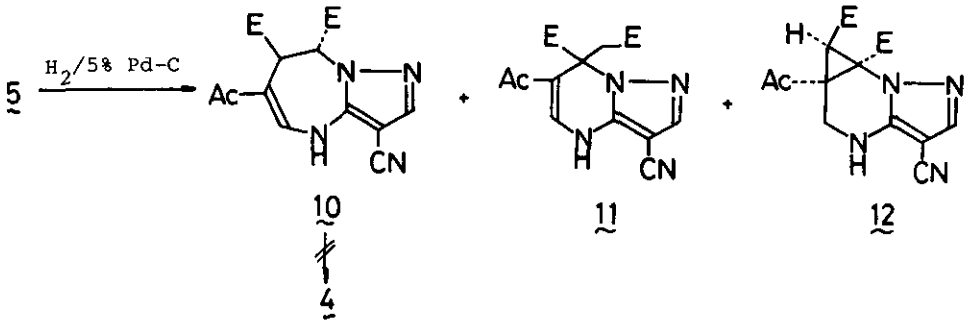
Reaction of 1 with ethyl diazoacetate under the same reaction conditions as reported before, followed by silica gel column chromatography, afforded the third compound (4) [3.8% yield, yellow needles, mp 214-215°C (from AcOEt-hexane), $C_{16}H_{16}N_4O_5$, ν max (KBr) : 3270 (NH), 2220 (CN), 1735 and 1645 (CO)]. Its PMR spectrum (DMSO-d_6)

displays a singlet at δ 7.10 (1H) in addition to signals at δ 8.30 (1H, s) and 9.88 (1H, br s, exchanged with D_2O). Based on these evidences coupled with UV spectrum [λ (EtOH) : 273 (4.25), 340 (3.78) and 420 (3.55)], compound 4 was determined as 6-acetyl-7,8-diethoxycarbonyl-4H-pyrazolo[1,5-a][1,3]diazepine-3-carbonitrile. When heated under reflux with ethyl diazoacetate in benzene, 1 gave 2 in 94% yield as a single product. In order to obtain the experimental evidence concerning the formation of 4, 2 was treated with silicic acid (Merk, PF254) in $CHCl_3$ under vigorous stirring for 2-3 days at room temperature. Separation of silicic acid and elution with $CHCl_3$ - MeOH (1 : 1) followed by evaporation left red needles (5) [70% yield, mp 236-239°C (from AcOEt), $C_{13}H_{12}N_4O_3$, ν max (KBr) : 3200 (NH), 2220 (CN), 1720 and 1660 (CO)], whose PMR spectrum revealed the disappearance of a $CO_2C_2H_5$ group and three singlet signals at δ 6.60, 7.69 and 8.00. In order to confirm the position of ethoxycarbonyl group on diazepine ring, the corresponding methyl ester (6), prepared by reaction of 1 with methyl diazoacetate, was treated with silicic acid in $CHCl_3$ to give red needles, which were identical with 5 by comparison of IR and PMR spectra.



From these results, the structure of 5 was established as 6-acetyl-8-ethoxycarbonyl-4H-pyrazolo[1,5-a][1,3]diazepine-3-carbonitrile, formed via 7 followed by ring expansion with decarboxylation. Refluxing 5 with methyl iodide in the presence of K_2CO_3 in acetone gave the N-methyl derivative (8) [δ (DMSO-d_6):3.49 (3H, s, NCH_3), 6.93 (1H, s, C_2-H), 7.39 (1H, s, C_5-H), and 8.18 (1H, s, C_7-H)]. Catalytic hydro-

genation (5% Pd-C) of 5 gave the tetrahydro derivative (9) as colorless needles. Then we have turned our attention to synthesize 4 according to the method for the preparation of 9H-imidazo[1,2-a][1,3]diazepines.[3] Catalytic hydrogenation (5% Pd-C) of 2 gave a mixture, from which three products (10, 11 and 12) were isolated in yields of 33, 44 and 3%, respectively. The structure of these products was mainly confirmed by PMR spectral data,[5] in which the stereochemistry of C_7- and C_8-substituents of 10 might be trans from the coupling constant (5 Hz) between C_7- and C_8-hydrogens. However, attempts to prepare the compound 4 from 10 failed.



ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. This paper constitutes Part V of a series of papers entitled "Ring Transformation of 6H-Cyclopropa[e]pyrazolo[1,5-a]pyrimidine". For Part IV, see T. Kurihara, K. Nasu and T. Tani, J. Heterocyclic Chem., 1982, 19, 519.

2. T. Kurihara, T. Tani, and K. Nasu, Chem. Pharm. Bull., 1981, 29, 1548 ; T. Kurihara, T. Tani, K. Nasu, M. Inoue, and T. Ishida, ibid., 1981, 29, 3214.

3. T. Kurihara, T. Tani, and K. Nasu, Heterocycles, 1981, 16, 1677.

4. T. Kurihara, K. Nasu, F. Ishimori, and T. Tani, J. Heterocyclic Chem., 1981, 19, 163.

5. 10 : mp 178-179°C, PMR (DMSO-d_6) δ : 1.00-1.10 (6H, m, 2 × $CO_2CH_2CH_3$), 2.27 (3H, s, $COCH_3$), 3.80-4.15 (4H, m, 2 × $CO_2CH_2CH_3$), 4.78 (1H, d, J=5 Hz, C_8-H), 5.95 (1H, d, J=5 Hz, C_7-H), 7.33 (1H, s, C_5-H), 7.83 (1H, s, C_2-H), 10.74 (1H, br s, NH).

   11 : mp 178-179°C, PMR (DMSO-d_6) δ : 1.00-1.20 (6H, m, 2 × $CO_2CH_2CH_3$), 2.25

(3H, s, $COCH_3$), 3.15 and 3.42 (each 1H, each d, $\underline{J}$=15 Hz, CH_2), 3.85 and 4.05 (each 2H, each q, $\underline{J}$=7 Hz, 2 × $CO_2\underline{CH}_2CH_3$), 7.75 and 7.90 (each 1H, each s, C_2- and/or C_5-H), 11.50 (1H, br s, NH).

12 : mp 170-172°C, PMR (DMSO-$\underline{d}_6$) δ : 1.13 (6H, t, $\underline{J}$=7 Hz, 2 × $CO_2CH_2\underline{CH}_3$), 2.33 (3H, s, $COCH_3$), 3.30 (1H, s, C_6-H), 3.58 and 3.73 (each 1H, each br s, CH_2), 3.85-4.25 (4H, m, 2 × $CO_2\underline{CH}_2CH_3$), 7.62 (1H, s, C_2-H), 7.90 (1H, br s, NH).

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