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Synthesis of 4,6-Disubstituted Dimethyl Pyridazine-3,5-dicarboxylates

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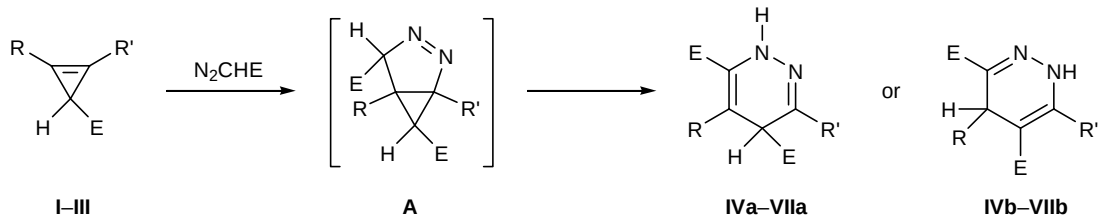
Abstract—Dimethyl pyridazine-3,5-dicarboxylates were synthesized by reaction of substituted 2-cyclopropenecarboxylates with methyl diazoacetate, followed by oxidation of the resulting 1,4-dihydropyridazine-4,6-dicarboxylates.

We proposed in [1] a procedure for the synthesis of substituted methyl pyridazine-4-carboxylates on the basis of cycloadducts derived from diazomethane and 2-cyclopropenecarboxylic acids. In the present work we applied an analogous scheme to obtain substituted dimethyl pyridazine-3,5-dicarboxylates using methyl diazoacetate instead of diazomethane. The initial compounds were known 2,3-disubstituted methyl 2-cyclopropenecarboxylates **I**–**III**. Cyclopropene **I** reacted with methyl diazoacetate at a much lower rate than with diazomethane; after 90 days at room temperature, the conversion was ~40%, whereas the reaction with diazomethane was complete in 10–12 days. We have found more appropriate conditions for the reaction of **I** with methyl diazoacetate: in dimethylformamide at 85°C, the reaction was complete in 30 h, and the product was formed in high yield. Both at room temperature and at 85°C, the same product was obtained, 1,4-dihydropyridazine **IVa**. Presumably [1], the corresponding bicyclic adduct **A** is formed initially, and its enhanced CH acidity favors the subsequent fast isomerization with cleavage of the three-membered carbon ring [2].

Like cyclopropene **I**, compounds **II** and **III** readily reacted with methyl diazoacetate at 75–80°C in DMF. From cyclopropene **II** we obtained 1,4-dihydropyridazine derivative **Va**, and compound **III** gave rise to two isomeric 1,4-dihydropyridazines **VIa** and **VIIa** at a ratio of 5:1. Obviously, compounds **Va**–**VIIa** are formed in a way similar to the formation of **IVa**, and the isomer ratio **VIa**:**VIIa** is determined by regioselectivity of the cycloaddition of methyl diazoacetate at the unsymmetrically substituted double bond of cyclopropene **III**. It should be noted that in the reaction with the same substrate (**III**), methyl diazoacetate shows a lower regioselectivity than diazomethane (the ratio of the isomeric adducts in the reaction with diazomethane was 11:1 [1]). However, the proposed scheme of formation of compounds **IVa**–**VIIa** cannot be regarded as an unambiguous proof for their structure. In fact, we showed in [1] that base-catalyzed isomerization of 2,3-diazabicyclo[3.1.0]hexenes like **A** can take two pathways leading to 1,4-dihydropyridazines **IVa**–**VIIa** and tautomeric structures **IVb**–**VIIb** (Scheme 1).

Analysis of the spectral data (Table 1) confirmed the 1,4-dihydropyridazine structure of compounds **Va**

Scheme 1.



I–**III** **A** **IVa**–**VIIa** **IVb**–**VIIb**

I–**VII**, E = COOMe; **I**, **IVa**, **IVb**, R = R' = Ph; **II**, **Va**, **Vb**, R = R' = Me; **III**, **VIa**, **VIb**, R = Me, R' = Ph; **III**, **VIIa**, **VIIb**, R = Ph, R' = Me.

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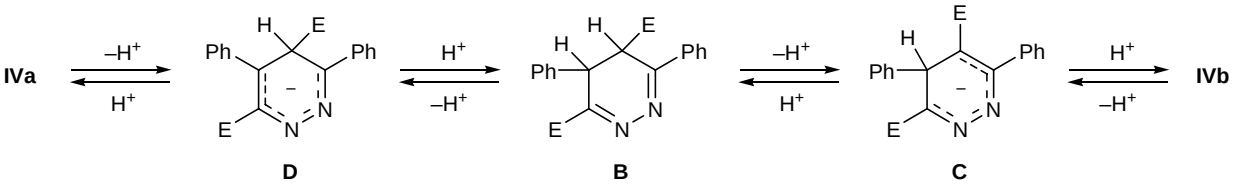
Scheme 2.

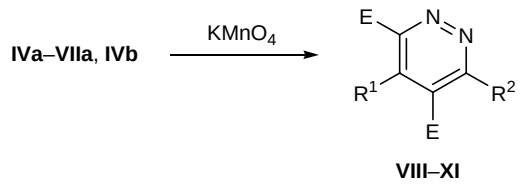


E = COOMe.

and **VIa**. Their ^{1}H NMR spectra contained singlets from the 4-H protons and protons of the methyl groups; alternative structures **Vb** and **VIb** should be characterized by splitting of the corresponding signals. It was more difficult to distinguish between structures **IVa/IVb** and **VIIa/VIIb** on the basis of the available spectral data. We have found that compound **IVa** undergoes isomerization into **IVb** by the action of sodium hydroxide in DMSO. The main difference between isomers **IVa** and **IVb** is the presence of a downfield (δ 7.8–8.0 ppm) two-proton signal in the ^{1}H NMR spectrum of **IVa**; no such signal was observed in the spectrum of **IVb**. This signal is typical of *ortho*-protons of the 3-phenyl group in **IVa** [1]. The choice between isomers **VIIa** and **VIIb** was made in favor of the former, taking into account that the chemical shifts of C^4 and C^5 in the ^{13}C NMR spectrum of **VIIa** were similar to those observed for **IVa** rather than **IVb**. Probably, the isomerization of **IVa** into **IVb** involves intermediate formation of 4,5-dihydropyridazine **B** via intermolecular proton transfer. The driving force of this process is likely to be clearly higher stability of anion **C** as compared to **D** (Scheme 2).*

1,4-Dihydropyridazines **IV**–**VII** were oxidized by the action of potassium permanganate in aqueous acetone. The reaction was fast, and the corresponding 4,6-disubstituted dimethyl pyridazine-3,5-dicarboxylates **VIII**–**XI** were obtained in high yields (Scheme 3). The ^{1}H and ^{13}C NMR spectra of compounds **VIII**–**XI** (Table 2) were consistent with the assumed structures.

Scheme 3.



E = COOMe; **VIII**, $R^1 = R^2$ = Ph; **IX**, $R^1 = R^2$ = Me; **X**, R^1 = Me, R^2 = Ph; **XI**, R^1 = Ph, R^2 = Me.

* We are now trying to prove the general character of prototropic isomerization in the series of 1,4-dihydropyridazines. Unfortunately, this work is complicated by high sensitivity of these compounds to oxidants (especially in alkaline medium).

The structure of regioisomers **X** and **XI** was proved by comparing their spectral parameters. First of all, these compounds were characterized by different chemical shifts of the methyl protons and carbon nuclei in the ^{1}H and ^{13}C NMR spectra: the corresponding signals in the spectra of **XI** were located in a weaker field due to effect of the neighboring azo group. Second, the signal from the *ortho*-protons of the phenyl group in **X** was displaced downfield for the same reason. We believe that these data are sufficient to distinguish between structures **X** and **XI**. In addition, we thus confirmed the assumed structures of parent compounds **VI** and **VII** and hence the regioselectivity of cycloaddition of methyl diazoacetate to cyclopropene **III**.

Taking into account accessibility of the initial cyclopropene derivatives, the proposed two-step procedure for the synthesis of 4,6-disubstituted pyridazine-3,5-dicarboxylates seems to be an efficient alternative to the known methods of preparation of pyridazine-3,5-dicarboxylic acids [3].

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer (300.13 and 75.47 MHz, respectively) from solutions in $CDCl_3$. The IR spectra were measured on a UR-20 instrument from 1% solutions in CCl_4. The elemental compositions were determined on an HP-185B CHN-analyzer. Silufol UV-254 plates were used for analytical thin-layer chromatography. The products were separated and purified by column chromatography on silica gel L 40/100 μm (Chemapol). Esters **I** [4], **II** [5], and **III** [6] were synthesized by known methods.

Dimethyl 3,5-diphenyl-1,4-dihydropyridazine-4,6-dicarboxylate (IV). *a*. A solution of 0.25 g

Table 1. ^{1}H and ^{13}C NMR spectra of 1,4-dihydropyridazines **IV**–**VII**

Comp. no.	^{1}H NMR spectrum, δ, ppm					^{13}C NMR spectrum, δ_C, ppm					
	4-H	CH_3	OCH_3	NH	Ph	C^4	C^5	CH_3	OCH_3	C=O	Ph, C^3, C^6
IV	4.87 s	–	3.69 s, 3.75 s	8.80 br.s	7.30–7.45 (8H), 7.80–7.90 (2H)	46.4	111.1	–	52.2, 52.7	163.3, 169.9	126.6 (2C), 127.6, 127.8 (2C), 127.9, 128.4 (2C), 129.0, 129.3 (2C), 134.6, 135.0, 137.9
IVa	4.99 s	–	3.76 s, 3.87 s	8.53 br.s	7.12–7.18 (3H), 7.18–7.24 (2H), 7.30–7.40 (5H)	41.9	103.1	–	52.5, 52.6	164.3, 171.0	126.7, 127.8 (2C), 128.9 (2C), 129.2, 129.4 (2C), 129.8 (2C), 133.7, 136.4, 137.0
V	3.77 s	2.11 s, 2.21 s	3.70 s, 3.85 s	7.87 br.s	–	50.3	111.2	18.4, 21.7	52.0, 52.3	162.9, 168.9	126.7, 136.3
VI	4.47 s	2.35 s	3.69 s, 3.88 s	8.47 br.s	7.35–7.45 (3H), 7.75–7.83 (2H)	46.9	112.3	18.5	52.0, 52.4	162.6, 169.4	125.9 (2C), 126.3, 128.2 (2C), 128.6, 134.1, 135.4
VII	4.14 s	2.22 s	3.65 s, 3.75 s	[a]	7.28–7.40	49.7	110.2	21.8	52.1, 52.5	163.5, 169.3	127.6, 127.7 (2C), 129.1 (2C), 129.2, 136.8, 137.9

[a] The NH signal was not detected in $CDCl_3$; in DMSO-d_6: δ 9.4 ppm, br.s.

Table 2. ^{1}H and ^{13}C NMR spectra of dimethyl pyridazine-3,5-dicarboxylates **VIII**–**XI**

Comp. no.	^{1}H NMR spectrum, δ, ppm			^{13}C NMR spectrum, δ_C, ppm				
	CH_3	OCH_3	Ph	C^3, C^6	CH_3	OCH_3	C=O	Ph, C^4, C^5
VIII	–	3.48 s, 3.81 s	7.30–7.40 (2H), 7.43–7.57 (6H), 7.73–7.80 (2H)	151.5, 157.6	–	52.6, 52.9	164.9, 165.5	127.9 (2C), 128.3 (2C), 128.6 (2C), 128.7 (2C), 129.4, 130.1, 131.8, 132.5, 135.4, 136.8
IX	2.47 s, 2.72 s	3.99 s, 4.03 s	–	151.1, 156.6	15.8, 20.4	52.9, 53.0	165.1, 166.1	133.2, 134.4
X	2.55 s	3.73 s, 4.06 s	7.46–7.53 (3H), 7.65–7.72 (2H)	151.1, 157.4	15.7	52.6, 53.0	164.9, 166.3	128.3 (2C), 128.5 (2C), 129.4, 130.9, 134.5, 136.3
XI	2.82 s	3.64 s, 3.78 s	7.23–7.30 (2H), 7.42–7.48 (3H)	151.5, 156.8	20.4	52.6, 52.8	165.0, 165.6	127.7 (2C), 128.4 (2C), 129.3, 132.1, 132.8, 135.9

(1 mmol) of compound **I** and 0.5 g (5 mmol) of methyl diazoacetate in 2 ml of DMF was kept for 30 h at 85°C under argon. The mixture was cooled and diluted with 3 ml of water, and the precipitate was filtered off and recrystallized from aqueous alcohol. Yield 0.29 g (84%), mp 139°C. IR spectrum (CCl_4), ν, cm^{-1}: 3415 (N–H); 2955 (C–H); 1746, 1719 (C=O). Found, %: C 68.48; H 5.28; N 7.91. $C_{20}H_{18}N_2O_4$. Calculated, %: C 68.55; H 5.18; N 8.00.

b. A solution of 0.5 g (2 mmol) of compound **I** and 0.5 g (5 mmol) of methyl diazoacetate in 2 ml of benzene was placed in an ampule, and the ampule was sealed and kept for 90 days at room temperature. The mixture was subjected to column chromatography using hexane–diethyl ehter (2:1) as eluent to isolate 0.32 g of initial compound **I**, R_f 0.42, and 0.15 g (21%) of compound **IVa**, R_f 0.12.

Dimethyl 4,6-diphenyl-1,4-dihydropyridazine-3,5-dicarboxylate (IVb). One drop of 50% aqueous potassium hydroxide was added to a solution of 50 mg (0.14 mmol) of compound **IVa** in 0.5 ml of dimethyl sulfoxide, the mixture was stirred for 5 h at room temperature and diluted with 15 ml of water, and the precipitate was filtered off. Yield 27 mg (54%), mp 153°C (from aqueous methanol). Found, %: C 68.55; H 5.27; N 7.82. $C_{20}H_{18}N_2O_4$. Calculated, %: C 68.56; H 5.18; N 8.00.

Dimethyl 3,5-dimethyl-1,4-dihydropyridazine-4,6-dicarboxylate (Va). A solution of 0.28 g (2.2 mmol) of compound **II** and 1.0 g (10 mmol) of

methyl diazoacetate in 5 ml of DMF was heated for 20 h at 75°C under argon. The solvent and excess methyl diazoacetate were removed under reduced pressure, and the residue was recrystallized from water. Yield 0.39 g (78%), mp 94°C. Found, %: C 53.16; H 6.21; N 12.38. $C_{10}H_{14}N_2O_4$. Calculated, %: C 53.09; H 6.24; N 12.38.

Reaction of ethyl 2-methyl-3-phenyl-2-cyclopropenecarboxylate (III) with methyl diazoacetate. A solution of 0.75 g (4 mmol) of compound **III** and 1.5 g (15 mmol) of methyl diazoacetate in 8 ml of DMF was heated for 25 h at 80°C under argon. The mixture was cooled, diluted with 60 ml of water, and extracted with methylene chloride (3×25 ml). The combined extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue, 1.31 g, was a mixture of compounds **VIa** and **VIIa** at a ratio of 5:1 (according to the ^{1}H NMR data). It was subjected to column chromatography using hexane–ethyl acetate–chloroform (3:1:1) as eluent.

Dimethyl 5-methyl-3-phenyl-1,4-dihydropyridazine-4,6-dicarboxylate (VIa). mp 101°C, R_f 0.15. IR spectrum (CCl_4), ν, cm^{-1}: 3405 (N–H); 2937 (C–H); 1741, 1715 (C=O). Found, %: C 62.56; H 5.64; N 9.66. $C_{15}H_{16}N_2O_4$. Calculated, %: C 62.49; H 5.59; N 9.72.

Dimethyl 3-methyl-5-phenyl-1,4-dihydropyridazine-4,6-dicarboxylate (VIIa). mp 95ºC, R_f 0.11. Found, %: C 62.38; H 5.62; N 9.68. $C_{15}H_{16}N_2O_4$. Calculated, %: C 62.49; H 5.59; N 9.72.

Oxidation of 1,4-dihydropyridazines IVa–VIIa (*general procedure***).** Powdered potassium permanganate, 1 mmol, was added in one portion to a solution of 1 mmol of 1,4-dihydropyridazine **IVa**–**VIIa** in aqueous acetone, and the mixture was stirred for 1–5 h until the initial compound disappeared (TLC). The precipitate of MnO_2 was filtered off and washed with acetone, the filtrate was evaporated, and the residue was purified by recrystallization or flash chromatography (compounds **X** and **XI**).

Dimethyl 4,6-diphenylpyridazine-3,5-dicarboxylate (VIII) was obtained from 1,4-dihydropyridazine **IVa**. Yield 83%, mp 133°C (from aqueous methanol). Found, %: C 68.79; H 4.77; N 7.80. $C_{20}H_{16}N_2O_4$. Calculated, %: C 68.96; N 4.63; N 8.04. According to the TLC data, the same product was formed by oxidation of **IVb**.

Dimethyl 4,6-dimethylpyridazine-3,5-dicarboxylate (IX) was obtained from 1,4-dihydropyridazine **Va**. Yield 77%, mp 97°C (from water). Found, %: C 53.57; H 5.38; N 12.37. $C_{20}H_{12}N_2O_4$. Calculated, %: C 53.57; H 5.40; N 12.50.

Dimethyl 4-methyl-6-phenylpyridazine-3,5-dicarboxylate (X) was obtained from 1,4-dihydropyridazine **VI**. Yield 91%, mp 70°C. Found, %: C 62.84; H 4.93; N 9.74. $C_{15}H_{14}N_2O_4$. Calculated, %: C 62.93; H 4.93; N 9.79.

Dimethyl 6-methyl-4-phenylpyridazine--3,5-dicarboxylate (XI) was obtained from 1,4-dihydropyridazine **VII**. Yield 88%, mp 64°C. Found, %: C 63.12; H 4.92; N 9.56. $C_{15}H_{14}N_2O_4$. Calculated, %: C 62.93; H 4.93; N 9.79.

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