A New Method for the Synthesis of Pyridine and Pyrido[3,4-*d*]Pyridazine Derivatives

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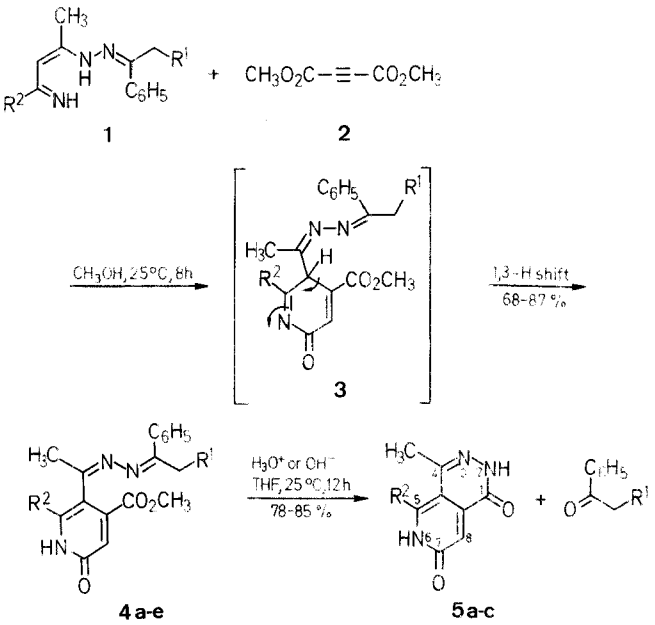
The reaction of equimolecular amounts of *N'*-(3-imino-1-alkenyl)hydrazones and dimethyl acetylenedicarboxylate affords functionalized 2(1*H*)-pyridinones. Treatment of these compounds with mineral acid or base yields the new 1,7-dioxo-1,2,6,7-tetrahydropyrido[3,4-*d*]pyridazines.

The usefulness of acetylenedicarboxylic esters for the synthesis of heterocyclic compounds has been widely demonstrated.[1] In earlier papers, we have described a new synthesis of pyridines[2] and 2(1*H*)-pyridinones[3] by reaction of 4-amino-1-azabutadienes with methyl acetylenedicarboxylate. This acetylenic compound reacts with 1,3,2-diazasilines to yield a new class of eight-membered heterocycles.[4]

Alkyl phenyl ketone *N'*-(3-imino-3-aryl-1-methyl-1-alkenyl)-hydrazones **1**, which are obtained by reaction of appropriate ketazines with saturated nitriles,[5] are suitable starting materials for the synthesis of new heterocycles.[5,6] We report here a new method to prepare 2-pyridinones by reaction of hydrazones **1** with dimethyl acetylenedicarboxylate **2**. Hydrolysis of the pyridine derivatives **4** thus obtained affords the new 1,7-dioxo-1,2,6,7-tetrahydropyrido[3,4-*d*]pyridazines **5** in high yield.

When the hydrazones **1** and dimethyl acetylenedicarboxylate **2** (mol ratio 1 : 1) were allowed to react in the absence of a catalyst under moderate conditions, 2(1*H*)-pyridinones **4** were always obtained in good yields (see Table 1). The formation of the heterocycles **4** can be explained through the addition of 2-CH of the enamine **1** to the acetylenic triple bond;[7] subsequent condensation of the imine NH with one of the two ester groups leads to the intermediate **3**, which in turn can undergo a 1,3-hydrogen shift to yield the heterocycle **4**. The proposed mechanism also accounts for the formation of dihydropyridines from 4-amino-1-azabutadienes.[3]



Heterocycles **4** were characterized on the basis of their microanalyses and spectral data. All compounds **4** display in their IR absorptions at $\nu \approx 3400$ (NH) and 1750 cm^{-1} (C=O). In the ^1H-NMR spectra, the appearance of a singlet centered at $\delta \approx 7$ ppm, which is assigned to the =CH grouping, is typically present. The ^{13}C-NMR spectra show four signals at $\delta = 167$ (s), 164 (s), 163 (s), and 159 (s) ppm which were assigned to the two carbonyl and two imine C-atoms.

Table 1. Yields and Physical Data of Compounds **4** and **5** Prepared

Compound	R^1	R^2	Yield (%)	m.p. (°C)	Molecular Formula[a]	MS *m/e* (M^+)
4a	H	C_6H_5	75	228–230	$C_{23}H_{21}N_3O_3$ (387.4)	387
4b	H	4-$(CH_3)C_6H_4$	80	235–236	$C_{24}H_{23}N_3O_3$ (401.5)	401
4c	H	4-(Cl)C_6H_4	68	226–227	$C_{23}H_{20}ClN_3O_3$ (421.9)	
4d	CH_3	4-$(CH_3)C_6H_4$	87	204–206	$C_{25}H_{25}N_3O_3$ (415.5)	415
4e	CH_3	4-(Cl)C_6H_4	85	170–172	$C_{24}H_{22}ClN_3O_3$ (435.9)	
5a	–	C_6H_5	85	343–345 (dec.)	$C_{14}H_{11}N_3O_2$ (253.3)	253
5b	–	4-$(CH_3)C_6H_4$	80	335–337 (dec.)	$C_{15}H_{13}N_3O_2$ (267.0)	267
5c	–	4-(Cl)C_6H_4	78	348–350 (dec.)	$C_{14}H_{10}ClN_3O_2$ (287.7)	287

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.36, H ±0.24, N ±0.29.

Table 2. Spectral Data of Compounds **4** and **5**

Compound	IR (KBr) ν (cm^{-1})	^1H-NMR (80 MHz, $CDCl_3$/TMS) δ (ppm)	^{13}C-NMR (20 MHz, $CDCl_3$/TMS) δ (ppm)
4a	1660, 1730, 3300	1.7 (s, CH_3); 2.1 (s, CH_3); 3.7 (s, CH_3); 6.7 (s, 3-H); 7.0–8.0 (m, 10 H_{arom})	165.8 (s), 160.8 (s), 148.2 (s), 143.8 (s), 136.8 (s), 133.0 (s), 128.9, 128.6, 127.9, 127.6, 126.5, 115.4 (d), 51.6 (q), 18.7 (q), 13.5 (q)
4b	1650, 1690, 3450	1.7 (s, CH_3); 2.1 (s, CH_3); 2.3 (s, CH_3); 3.7 (s, CH_3); 6.7 (s, 3-H); 6.9–8.0 (m, 9 H_{arom})	166.8 (s), 163.5 (s), 159.6 (s), 146.6 (s), 145.5 (s), 140.4 (s), 138.1 (s), 129.5, 128.6, 128.1, 127.8, 126.6, 118.9 (d), 52.5 (q), 21.3 (q), 19.8 (q), 14.8 (q)
4c	1620, 1690, 1760, 3450	2.1 (s, CH_3); 2.6 (s, CH_3); 4.5 (s, CH_3); 8.1 (s, 3-H); 8.5–9.5 (m, 9 H_{arom})	169.7 (s), 163.9 (s), 162.8 (s), 157.7 (s), 145.7 (s), 136.6 (s), 132.0 (s), 130.7 (s), 129.9, 129.3, 129.0, 128.4, 128.2, 126.9, 119.7 (d), 51.7 (q), 20.0 (q), 14.9 (q)
4d	1630, 1720, 3430	1.1 (t, CH_3); 1.8 (s, CH_3); 2.4 (s, CH_3); 2.7 (q, CH_2); 3.8 (s, CH_3); 6.7 (s, 3-H); 7.0–8.1 (m, 9 H_{arom})	166.7 (s), 163.8 (s), 163.7 (s), 159.7 (s), 146.6 (s), 145.7 (s), 140.3 (s), 136.8 (s), 129.9, 129.4, 128.6, 126.8, 118.7 (d), 52.5 (q), 21.5 (t), 21.0 (q), 19.8 (q), 11.7 (q)
4e	1650, 1720, 3250	1.1 (t, CH_3); 1.8 (s, CH_3); 2.7 (q, CH_2); 3.7 (s, CH_3); 6.7 (s, 3-H); 6.9–8.0 (m, 9 H_{arom})	166.1 (s), 164.1 (s), 163.6 (s), 159.1 (s), 145.3 (s), 136.6 (s), 136.5 (s), 136.2 (s), 131.3 (s), 130.2, 129.5, 128.9, 128.1, 126.1, 126.8, 119.3 (d), 52.5 (q), 21.6 (t), 21.4 (q), 11.6 (q)
5a	1660, 3100	1.7 (s, CH_3); 7.1 (s, 8-H); 7.3–7.8 (m, 5 H_{arom}); 11.5 (s, NH)	162.1 (s), 157.7 (s), 156.7 (s), 142.1 (s), 138.0 (s), 137.7 (s), 129.4, 129.1, 128.0, 106.7 (d), 23.1 (q)
5b	1660, 3200	1.8 (s, CH_3); 2.6 (s, CH_3); 7.3 (s, 8-H); 7.5–7.8 (m, 4 H_{arom}); 12.5 (s, NH)	162.0 (s), 157.8 (s), 155.7 (s), 142.2 (s), 139.1 (s), 138.1 (s), 134.0 (s), 129.3, 128.6, 108.0 (d), 23.2 (q), 21.0 (q)
5c	1670, 3200	1.7 (s, CH_3); 7.1 (s, 8-H); 7.3–7.7 (m, 9 H_{arom}); 11.5 (s, NH)	162.3 (s), 157.8 (s), 155.1 (s), 141.9 (s), 138.1 (s), 136.6 (s), 134.3 (s), 131.1, 128.1, 106.9 (d), 23.5 (q)

Hydrolysis of 2(1*H*)-pyridinones **4** with 2 molar sulfuric acid or 6 molar potassium hydroxide in tetrahydrofuran at room temperature resulted in a new method for the preparation of 1,7-dioxo-1,2,6,7-tetrahydropyrido[3,4-*d*]pyridazines **5** which are of interest because of their biological properties.[8]

The structure of compounds **5** was ascertained by microanalytical, mass spectrometric, and spectroscopic data. The IR spectra display two clear absorptions at $\nu = 3200$ and 1670 cm^{-1}, which are assigned to the N–H and C=O vibrations. In the ^{1}H-NMR spectra, the singlet centered at $\delta \approx 7$ ppm can be assigned to the =CH grouping. In the ^{13}C-NMR spectra, the signal of the same CH group is found at $\delta = 107$ ppm (doublet in off-resonance experiments); other typical signals are those corresponding to the carbonyl groups at $\delta \approx 162$ (s) and 158 (s) ppm and the C=N double bond at $\delta = 157$ (s) ppm.

In conclusion, the high yields combined with the ready availability of the starting materials make the present synthesis a convenient route to heterocycles **4** and **5**.

2(1*H*)-Pyridinones 4; General Procedure:

Dimethyl acetylenedicarboxylate (**2**; 1.42 g, 10 mmol) is added to a solution of the hydrazone **1** (10 mmol) in anhydrous methanol (60 ml). The mixture is stirred at room temperature for 8 h. Methanol is then evaporated and the residue is purified by recrystallization from hot hexane/chloroform.

1,7-Dioxo-1,2,6,7-tetrahydropyrido[3,4-*d*]pyridazines 5; General Procedure:

To a solution of the respective 2(1*H*)-pyridinone **4** (10 mmol) in tetrahydrofuran (50 ml), 2 molar sulfuric acid (30 ml) is added. After having been stirred at room temperature for 12 h, the mixture is poured into ice/water (200 ml). The aqueous organic layer is extracted with ether (100 ml); the organic phase is dried over sodium sulfate, filtered, and evaporated and the residue is recrystallized from ethanol.

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