An Efficient Synthesis of Novel Hexahydropyrido[2,3-*d*]pyrimidine Derivatives from (Arylmethylidene)pyruvic Acids (=(3*E*)-4-Aryl-2-oxobut-3-enoic Acids in Aqueous Media

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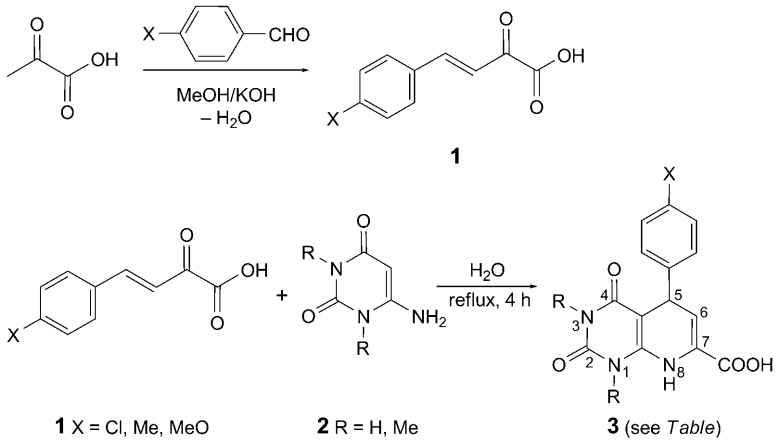
A series of new hexahydropyrido[2,3-*d*]pyrimidine derivatives **3** were synthesized by the cyclocondensation reaction of (arylmethylidene)pyruvic acids (=(3*E*)-4-aryl-2-oxobut-3-enoic acids) **1** and 6-aminouracils (=6-aminopyrimidine-2,4(1*H*,3*H*)-diones) **2** in H_2O under reflux conditions (*Scheme 1*, *Table*). This novel protocol has the advantages of facility, of easy workup, of high yields, and of an environmentally benign procedure. The structures of compounds **3a**–**3f** were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS). A plausible mechanism for the reaction is proposed (*Scheme 2*).

Introduction. – The compounds which possess a dihydropyridopyridine framework in their structure have been recognized both in medicinal [1] and in synthetic chemistry [2–4] due to their unique properties. Syntheses of pyridopyrimidine derivatives are of considerable interest as they have a wide range of biological properties such as antibacterial [5], antiasthmatic, antiallergic [6], antifolate [7], tyrosine-kinase [8], antimicrobial [9], calcium-channel-antagonist [10], anti-inflammatory and analgesic [11], antihypertensive [12], antileishmanial [13], tuberculostatic [14], anticonvulsant [15], diuretic and potassium-sparing [16], and antiaggressive [17] activities.

With the aim of developing more efficient synthetic methods, improving the bond-forming efficiency (BFE), and in continuation of our previous work on the cyclocondensation reactions, which were performed in H_2O successfully [18], we now report our study about the reaction of (arylimethylidene)pyruvic acids (=(3*E*)-4-aryl-2-oxobut-3-enoic acids) **1** with 6-aminouracils (=6-aminopyrimidine-2,4(1*H*,3*H*)-diones) **2** as highly reactive heterocyclic C-nucleophiles. This approach allowed us to prepare the previously unknown hexahydropyrido[2,3-*d*]pyrimidine derivatives **3** (*Scheme 1*). Besides their potential biologic activities, the produced target compounds **3**, as heterocyclic α-amino-α,β-unsaturated carboxylic acids, can be of interest for the synthesis of novel peptides containing a heterocyclic moiety in their skeleton, which could lead to some biologically active compounds. On the other hand, compounds **3** can be used as efficient starting materials for further multicomponent reactions due to the presence of both an amine and a carboxylic acid functional group.

Because of the toxic and volatile nature of many organic solvents, the use of H_2O as a solvent medium is of interest. Compared with organic solvents, H_2O has advantages

Scheme 1



such as safety, low cost, and environmentally friendly processes [19]. These facts prompted us to use H_2O as solvent in the synthesis of **3** from **1** and **2**.

Results and Discussion. – In the cyclocondensation reaction of *Scheme 1*, (arylmethylidene)pyruvic acid **1** plays an important role as an attractive starting material for the following reasons: *a*) it has a higher reactivity in comparison to usual α,β-unsaturated ketones, *b*) it contains active functional groups which can be used for further synthesis, and *c*) its preparation is easy, *i.e.*, the acids **1** were synthesized according to the known procedure [20] by reaction of aromatic aldehydes and pyruvic acid in an aqueous MeOH solution of KOH (*Scheme 1*). The subsequent cyclocondensation of **1** with the uracils **2** to give the 5-aryl-1,2,3,4,5,8-hexahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylic acids **3a**–**3f** in high yields (89–95%) was carried out in aqueous medium under reflux conditions for 4 h (*Table*).

Table. *Synthesis of Hexahydropyrido[2,3-*d*]pyrimidines* **3a**–**3f** *in Aqueous Medium*

Product	X	R	M.p. [°]	Yield [%][a])	Product	X	R	M.p. [°]	Yield [%][a])
3a	Cl	H	319–320	95	**3d**	Cl	Me	236–238	91
3b	MeO	H	315–316	90	**3e**	MeO	Me	228–229	89
3c	Me	H	298–299	93	**3f**	Me	Me	248–249	94

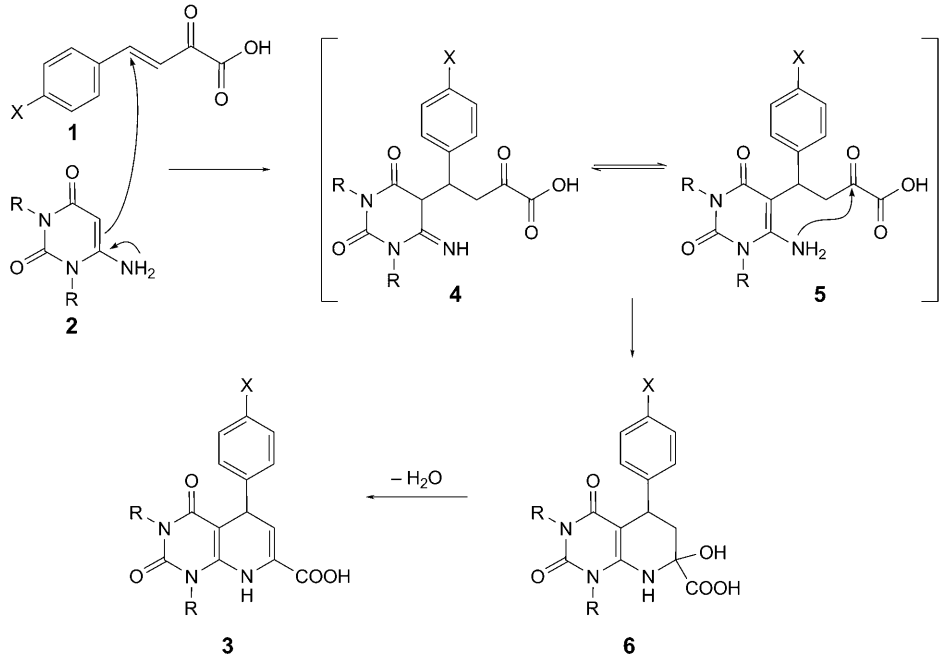
[a]) Yields refer to pure isolated products characterized by IR, ^{1}H- and ^{13}C-NMR spectroscopy, and mass spectrometry.

Although several approaches have been developed for the synthesis of the pyridopyrimidines, *e.g.*, *a*) the reaction of benzylidene derivatives of malononitrile with 3,4-dihydropyrimidin-6-amine in boiling EtOH [2], *b*) the three-component reaction of aldehydes, alkyl nitriles, and pyrimidinamines in H_2O and in the presence of KF/Al_2O_3 as catalyst [3][21], or *c*) the similar three-component reaction catalyzed by TEBAC

(= $PhCH_2NEt_3 \cdot Cl$) [4], our new procedure is simple and occurs under milder reaction conditions.

Considering the model of similar reactions for the synthesis of pyridopyrimidines, including nucleophilic attack of a nucleophilic C-atom of the pyrimidine rings to the α,β-unsaturated system [2–4], a plausible mechanism is proposed in *Scheme 2*. Due to the C-nucleophilic character of 6-aminouracils, it is reasonable to assume that **3** can be formed *via* the initial *Michael* addition of 6-aminouracil **2** to (arylmethylidene)pyruvic acid **1** to generate the *Michael* adduct **4**, which is isomerized under the reaction conditions to yield **5**. Intramolecular cyclization of **5** gives **3** after dehydration of intermediate **6** (*Scheme 2*).

Scheme 2. *Possible Mechanism for the Formation of Hexahydropyrido[2,3-*d*]pyrimidine Derivatives*



The structures of compounds **3a**–**3f** were deduced from their ^{1}H- and ^{13}C-NMR, IR, and MS data (see *Exper. Part*) and the NMR spectra. All products **3a**–**3f**, showed a characteristic *s* for H–C(5) at δ(H) 4.51–4.69 and a peak for C(5) at δ(C) 36.4–37.7. The MS displayed corresponding molecular-ion peaks.

In summary, we introduced an efficient method for the preparation of new hexahydropyrido[2,3-*d*]pyrimidine derivatives. Besides the simplicity of the method, our synthesized heterocyclic molecules have the potential to be biologically active or to be used as precursors to produce other biologically active compounds. Further investigations about the use of these product for the synthesis of novel compounds is going on in our laboratory.

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Experimental Part

General. All chemical materials used in this work were purchased from *Merck* and *Fluka* and used without further purification. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *ABB-FT-IR* (*FTLA 2000*) spectrometer; $\tilde{\nu}$ in cm^{1-}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-DRX-300 Avance* at 300 and 75 MHz, resp.; in (D_6)DMSO, δ in ppm rel. to Me_4Si, as internal standard, J in Hz. MS: *GC-MS-Hewlett-Packard* (EI, 70 eV) instrument.

Preparation of Compounds **3a**–**3f**: *General Procedure.* A mixture of the appropriate (arylmethylidene)pyruvic acid **1** (1 mmol) and 6-aminouracil or 6-amino-1,3-dimethyluracil **2** (1 mmol) in H_2O (15 ml) was heated to reflux for 4 h. After cooling, the formed precipitate was isolated by filtration and purified by washing with cold 50% aq. EtOH to afford the corresponding products in high yields.

*5-(4-Chlorophenyl)-1,2,3,4,5,8-hexahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylic Acid* (**3a**): Yield 303 mg (95%). White powder. M.p. 319–320°. IR (KBr): 3344 (NH), 3242 (COOH), 1733 (COOH), 1659 (NCO), 1621 (NCON), 1544 (arom.). ^{1}H-NMR: 4.60 (*d*, *J* = 5.3, H–C(5)); 5.86 (*dd*, *J* = 5.3, 1.2, H–C(6)); 7.24 (*d*, *J* = 8.5, 2 arom. H); 7.32 (*d*, *J* = 8.5, 2 arom. H); 8.15 (*s*, NH); 9.91 (*s*, NH); 10.47 (*s*, NH); 13.43 (br. *s*, COOH). ^{13}C-NMR: 36.9; 83.7; 113.7; 126.4; 128.2; 129.3; 131.0; 144.8; 145.9; 149.7; 162.9; 163.2. EI-MS (70 eV): 319 (3, M^+), 264 (28), 238 (28), 97 (57), 83 (68), 77 (16), 69 (80), 57 (100), 43 (94). Anal. calc. for $C_{14}H_{10}ClN_3O_4$ (319.75): C 52.60, H 3.15, N 13.14; found: C 52.50, H 3.10, N 13.08.

*1,2,3,4,5,8-Hexahydro-5-(4-methoxyphenyl)-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylic Acid* (**3b**): Yield 284 mg (90%). White powder. M.p. 315–316°. IR (KBr): 3344 (NH), 3242 (COOH), 1730 (COOH), 1658 (NCO), 1617 (NCON), 1544 (arom.). ^{1}H-NMR: 3.70 (*s*, MeO); 4.51 (*d*, *J* = 5.4, H–C(5)); 5.87 (*dd*, *J* = 5.4, 1.0, H–C(6)); 6.83 (*d*, *J* = 8.6, 2 arom. H); 7.12 (*d*, *J* = 8.6, 2 arom. H); 8.10 (*s*, NH); 9.90 (*s*, NH); 10.43 (*s*, NH); 13.40 (br. *s*, COOH). ^{13}C-NMR: 36.4; 55.1; 84.2; 113.8; 114.7; 125.7; 128.5; 138.2; 145.7; 149.8; 157.9; 163.0; 163.5. EI-MS (70 eV): 315 (5, M^+), 313 (49), 297 (9), 269 (100), 207 (41), 163 (82), 108 (92), 77 (25), 43 (16). Anal. calc. for $C_{15}H_{13}N_3O_5$ (315.28): C 57.14, H 4.16, N 13.33; found: C, 57.09; H, 4.13; N, 13.30.

*1,2,3,4,5,8-Hexahydro-5-(4-methylphenyl)-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylic Acid* (**3c**): Yield 278 mg (93%). White powder. M.p. 298–299°. IR (KBr): 3344 (NH), 3245 (COOH), 1729 (COOH), 1659 (NCO), 1621 (NCON), 1545 (arom.). ^{1}H-NMR: 2.24 (*s*, Me); 4.52 (*d*, *J* = 5.4, H–C(5)); 5.85 (*d*, *J* = 5.4, H–C(6)); 7.08 (br. *s*, 4 arom. H); 8.09 (*s*, NH); 9.88 (*s*, NH); 10.41 (*s*, NH); 14.35 (br. *s*, COOH). ^{13}C-NMR: 20.5; 36.8; 83.9; 114.5; 125.8; 127.2; 128.9; 135.3; 142.9; 145.7; 149.7; 162.9; 163.3. EI-MS (70 eV): 299 (14, M^+), 297 (56), 252 (100), 208 (21), 164 (22), 91 (15), 77 (9), 43 (6). Anal. calc. for $C_{15}H_{13}N_3O_4$ (299.28): C 60.20, H 4.38, N 14.04; found: C 60.12, H 4.30, N 14.00.

*5-(4-Chlorophenyl)-1,2,3,4,5,8-hexahydro-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylic Acids* (**3d**): Yield 316 mg (91%). White powder. M.p. 236–238°. IR (KBr): 3358 (NH), 3426 (COOH), 1701 (COOH), 1677 (NCO), 1620 (NCON), 1598 (arom.). ^{1}H-NMR: 3.07 (*s*, MeN); 3.44 (*s*, MeN); 4.69 (*d*, *J* = 5.4, H–C(5)); 6.00 (*d*, *J* = 5.4, H–C(6)); 7.25 (*d*, *J* = 8.5, 2 arom. H); 7.33 (*d*, *J* = 8.5, 2 arom. H); 7.63 (*s*, NH); 13.57 (br. *s*, COOH). ^{13}C-NMR: 27.5; 29.1; 37.7; 85.1; 115.1; 126.7; 128.3; 129.3; 131.1; 144.7; 145.7; 150.7; 160.8; 163.4. EI-MS (70 eV): 349 (7, $[M+2]^+$), 347 (22, M^+), 301 (31), 236 (100), 218 (63), 190 (91), 133 (28), 77 (4), 57 (4). Anal. calc. for $C_{16}H_{14}ClN_3O_4$ (347.80): C 55.26, H 4.06, N 12.08; found: C 55.18, H 4.00, N 12.02.

*1,2,3,4,5,8-Hexahydro-5-(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylic Acids* (**3e**): Yield 305 mg (89%). White powder. M.p. 228–229°. IR (KBr): 3411 (NH), 3366 (COOH), 1701 (COOH), 1669 (NCO), 1627 (NCON), 1598 (arom.). ^{1}H-NMR: 3.07 (*s*, MeN); 3.44 (*s*, MeN); 3.69 (*s*, MeO); 4.60 (*d*, *J* = 5.5, H–C(5)); 5.99 (*d*, *J* = 5.5, H–C(6)); 6.82 (*d*, *J* = 8.6, 2 arom. H); 7.12 (*d*, *J* = 8.6, 2 arom. H); 7.58 (*s*, NH); 13.50 (br. *s*, COOH). ^{13}C-NMR: 27.5; 29.0; 37.2; 55.0; 85.7; 113.7; 116.0; 126.2; 128.4; 138.0; 145.4; 150.7; 157.9; 160.8; 163.5. EI-MS (70 eV): 343 (50, M^+), 297 (100), 236 (83), 218 (70), 190 (99), 133 (32), 77 (12), 57 (6). Anal. calc. for $C_{17}H_{17}N_3O_5$ (343.34): C 59.47, H 4.99, N 12.24; found: C 59.40, H 4.93, N 12.18.

*1,2,3,4,5,8-Hexahydro-1,3-dimethyl-5-(4-methylphenyl)-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylic acids* (**3f**): Yield 307 mg (94%). White powder. M.p. 248–249°. IR (KBr): 3423 (NH), 3358 (COOH), 1701 (COOH), 1669 (NCO), 1618 (NCON), 1596 (arom.). ^{1}H-NMR: 2.23 (*s*, Me); 3.07 (*s*, MeN); 3.44 (*s*, MeN); 4.62 (*d*, $J = 5.5$, H–C(5)); 5.99 (*d*, $J = 5.5$, H–C(6)); 7.06 (*d*, $J = 8.3$, 2 arom. H); 7.11 (*d*, $J = 8.3$, 2 arom. H); 7.58 (*s*, NH); 13.50 (br. *s*, COOH). ^{13}C-NMR: 20.6; 27.5; 29.1; 37.7; 85.6; 116.0; 126.3; 127.3; 128.9; 135.5; 142.9; 145.5; 150.7; 160.8; 163.5. EI-MS (70 eV): 327 (35, M^+), 281 (42), 236 (100), 218 (72), 190 (90), 133 (29), 77 (5), 57 (3). Anal. calc. for $C_{17}H_{17}N_3O_4$ (327.34): C 62.38, H 5.23, N 12.84; found: C 62.30, H 5.20, N 12.79.

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