Synthesis of 4-Aryl-4,6-dihydropyrimido[4,5-*d*]pyridazine-2,5(1*H*,3*H*)-diones from *Biginelli* Compounds

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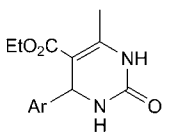
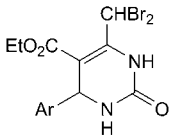
Biginelli compounds **1** were first brominated at Me–C(6) with 2,4,4,6-tetrabromocyclohex-2,5-dien-1-one to give Br_2CH–C(6) derivatives **2**. The hydrolysis of the 6-(dibromomethyl) group of **2c** to give the 6-formyl derivative **3c** in the presence of an expensive Ag salt followed by reaction with $N_2H_4 \cdot H_2O$ yielded tetrahydropyrimido[4,5-*d*]pyridazine-2,5(1*H*,3*H*)-dione (**4c**; *Scheme 1*). However, treatment of the 6-(dibromomethyl) derivatives **2** directly with $N_2H_4 \cdot H_2O$ led to the fused heterocycles **4** in better overall yield (*Schemes 1* and *2*; *Table*).

Introduction. – The *Biginelli* condensation [1][2] is an important multicomponent reaction that yields compounds with a dihydropyrimidine core. These compounds are reported to have useful pharmacological and other biological activities [3][4]. The parent *Biginelli* products of type **1** have several functionalities that could be modified easily, and numerous derivatives have been prepared for evaluation as drugs and compounds with other biological functions [3]. Several products were synthesized *via* 6-(monobromomethyl) derivatives [5–9] and only one *via* a 6-(dibromomethyl) derivative of type **2** [10]. We decided to prepare some useful derivatives *via* the corresponding 6-formyl compound. But the direct oxidation of Me–C(6) of **1** to a CHO group with SeO_2 was not successful [11]. We expected that this could be done *via* the $CHBr_2$ derivative **2**. Thus, syntheses of some fused N-heterocycles from these 6-(dibromomethyl) derivatives **2** or the corresponding aldehydes were undertaken.



1a Ar = Ph
1b Ar = 4-Cl–C_6H_4
1c Ar = 4-Br–C_6H_4
1d Ar = 4-Me–C_6H_4
1e Ar = 4-MeO–C_6H_4
1f Ar = Coumarin-6-yl



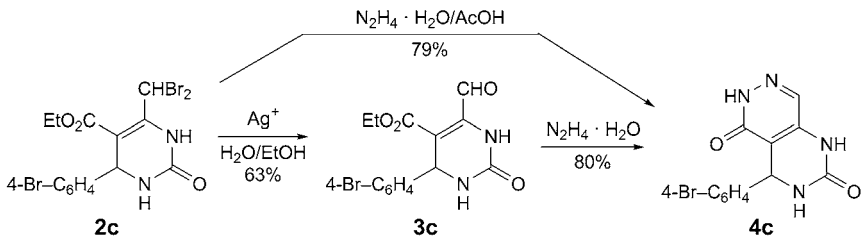
2a Ar = Ph
2b Ar = 4-Cl–C_6H_4
2c Ar = 4-Br–C_6H_4
2d Ar = 4-Me–C_6H_4
2e Ar = 4-MeO–C_6H_4
2f Ar = Coumarin-6-yl

Results and Discussion. – Initially, we used Br_2 in $CHCl_3$ and in AcOH, respectively, for the bromination of the *Biginelli* compounds **1** to give **2** [8][12][13]. The reactions gave incomplete conversion and resulted in mixtures of monobromo and dibromo products along with some unreacted starting material, even after a considerable period

of time and in the presence of excess Br_2. We obtained better yields of the 6-(dibromomethyl) derivatives **2** from the *Biginelli* compounds **1** by means of 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one (TBCO) as bromination reagent [14]. As an example, the *Biginelli* product **1d** furnished 65% of dibromo product **2d** and 16% of monobromo compound when treated with Br_2 in $CHCl_3$ or AcOH. But **1d** afforded the same two products in 86 and 8% yield, respectively, on treatment with 2.2 equiv. of TBCO in CH_2Cl_2.

First, we tried to convert dibromo derivative **2c** into formyl derivative **3c** by alkaline hydrolysis. However, the method was unsuccessful. However, we succeeded in hydrolyzing **2c** in the presence of AcOAg; the formyl derivative **3c** was then treated with $N_2H_4 \cdot H_2O$ to obtain the targeted 4-(4-bromophenyl)-4,6-dihydro-pyrimido[4,5-*d*]pyridazine-2,5-(1*H*,3*H*)-dione (**4c**) in an overall yield of 50.4% (*Scheme 1*). We then treated **2c** directly with $N_2H_4 \cdot H_2O$ and isolated **3c** in a much better yield (79%; *Scheme 1*).

Scheme 1



We then tested successfully the generality of the method with a few more 6-(dibromomethyl) derivatives **2** (see *Table*). The protocol failed only in the case of compound **2f** having a coumarin-6-yl (=2-oxo-2*H*-1-benzopyran-6-yl) substituent at C(4): a complex mixture resulted, possibly because of the involvement of the lactone ring of the coumarin-6-yl group.

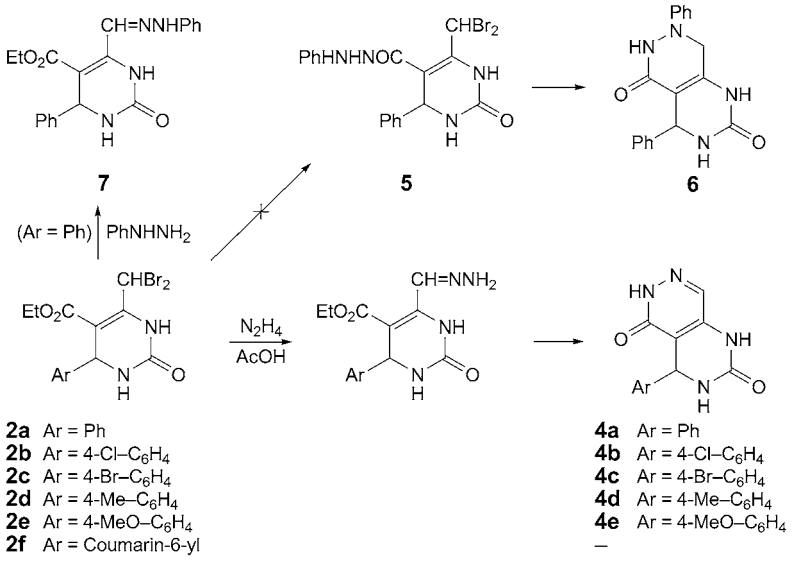
Table. *Synthesis of Pyrimidopyridazinediones* **4** from **2**: *Reaction Conditions* (EtOH, AcOH, reflux) *and Yield*

Substrate	Reflux time [h]	Product	R_f (solvent)of **4**	Yield [%]
2a	8	**4a**	0.5 (2% MeOH/AcOEt)	74
2b	7	**4b**	0.4 (80% AcOEt/Petroleum ether)	75
2c	7	**4c**	0.45 (80% AcOEt/Petroleum ether)	79
2d	9	**4d**	0.5 (80% AcOEt/Petroleum ether)	82
2e	10	**4e**	0.5 (70% AcOEt/Petroleum ether)	57

In view of the report [15] on the reaction of $N_2H_4 \cdot H_2O$ at the CO_2Et group of *Biginelli* compounds, we decided to test whether phenylhydrazine reacts with the 6-(dibromomethyl) derivative **2a** to yield **5** and then a cyclized product **6** (*Scheme 2*). But none of these products was formed; instead the hydrazone derivative **7** was obtained. From this result it may be concluded that $N_2H_4 \cdot H_2O$ first reacts with the $CHBr_2$ group,

and then the intramolecular condensation with CO_2Et takes place resulting in the formation of the condensed heterocycles **4** (*Scheme 2*).

Scheme 2



Conclusions. – An easy and efficient route to 4-aryl-4,6-dihydropyrimido[4,5-*d*]pyridazine-2,5-(1*H*,3*H*)-diones was established starting with the *Biginelli* compounds **1** *via* TBCO-assisted bromination followed by reaction with $N_2H_4 \cdot H_2O$.

The authors are very grateful to the *UGC* for a minor research grant.

Experimental Part

General. Materials were used as received from the commercial suppliers. M.p.: determined in a metal bath; uncorrected. IR Spectra: *Spectrum-2* (*Perkin-Elmer*) spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker* instruments; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. LC/MS: *Micromass* (*Water*) apparatus; in *m*/*z*. HR-MS: **4a**: *Micromass-Q-TOF* spectrometer (for **4a**) and *Micro-TOF-Q-II-10320* spectrometer (for **2d**); in *m*/*z*. Elemental analyses: *Thermo-Finnigan-Flash-EA-1112* analyzer.

6-(Dibromomethyl) Derivatives **2**: *Typical Procedure* [14]. To a soln. of **1d** (2 mmol) in dry CH_2Cl_2 (*ca*. 10 ml), a soln. of TBCO (6.6 mmol) in dry CH_2Cl_2 (*ca*. 10 ml) was added slowly while stirring. Stirring was continued for *ca*. 45 min during which almost complete conversion occurred. A little more solvent was added, and the mixture was washed free from tribromophenol by repeated washings with aq. K_2CO_3 soln. The org. layer was dried (Na_2SO_4) and slowly concentrated to give crystals. The solid was recrystallized from $CHCl_3$ to give pure **2d** (86%). From the mother liquor, the monobromo compound was obtained (8%).

Data of Ethyl 6-(Dibromomethyl)-1,2,3,4-tetrahydro-4-(4-methylphenyl)-2-oxopyrimidine-5-carboxylate (**2d**): IR (KBr): 3413 (br.), 1722, 1661, 502. ^1H-NMR (500 MHz, $CDCl_3$): 8.02 (*s*, 1 H); 7.12–7.19 (*AB*, *q*, 4 H); 6.99 (*s*, 1 H); 5.34 (*d*, *J* = 2.5, 1 H); 5.30 (*s*, 1 H); 4.13 (*q*, *J* = 7, 2 H); 2.33, (*s*, 3 H); 1.19 (*t*, *J* = 7, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 163.88; 152.39; 144.12; 139.25; 138.30; 129.61; 126.55; 100.49; 61.25; 55.10; 31.95; 21.10; 13.89. LC/MS: 452.99 ($[M+23]^+$), 455, and 456.99 in the intensity ratio 1 : 2 : 1.

HR-MS: 430.9586, 432.9585, and 434.9567 ($[M+1]^+$, $C_{15}H_{17}Br_2N_2O_3^+$) in the intensity ratio of 1:2:1; calc. 430.9600, 432.9581, and 434.9560.

Fused Heterocycles **4**: *General Procedure.* To a soln. of **2** (1 mmol) in EtOH (15–20 ml), $N_2H_4 \cdot H_2O$ (80%, *ca.* 1.5 mmol) was added followed by 5–8 drops of glacial AcOH. The mixture was heated under reflux for 6–10 h (TLC monitoring). Then, the mixture was diluted with H_2O (*ca.* 25 ml), neutralized with $NaHCO_3$, and then extracted with AcOEt (3 × 15 ml). The combined extract was dried (Na_2SO_4) and concentrated and the residue subjected to column chromatography (silica gel, 230–400 mesh). The products **4** were eluted with petroleum ether/AcOEt 2:3 to 1:4. For R_f values and yields, see *Table.*

*4,6-Dihydro-4-phenylpyrimido[4,5-*d*]pyridazine-2,5-(1*H*,3*H*)-dione* (**4a**): M.p. 335° (MeOH). IR (KBr): 3412, 3172, 1678, 1643. ^{1}H-NMR (400 MHz, $CDCl_3$): 12.56 (*s*, 1 H); 9.70 (*s*, 1 H); 7.91 (*s*, 1 H); 7.59–7.63 (*m*, 2 H); 7.33–7.36 (*m*, 2 H); 7.15–7.25 (*m*, 2 H); 5.42 (*d*, *J* = 3.0, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 159.01; 151.95; 142.90; 138.77; 129.02; 128.45; 127.67; 126.28; 110.76; 52.07. HR-MS: 243.0877 ($[M+1]^+$, $C_{12}H_{11}N_4O_2^+$; calc. 243.0822).

*4-(4-Chlorophenyl)-4,6-dihydropyrimido[4,5-*d*]pyridazine-2,5-(1*H*,3*H*)-dione* (**4b**): M.p. 343–44° (MeOH). IR (KBr): 3249 (br.), 1702, 1647, 1621, 1259, 540. ^{1}H-NMR (600 MHz, $CDCl_3$): 12.76 (*s*, 1 H); 9.81 (*s*, 1 H); 7.87 (*s*, 1 H); 7.61 (*s*, 1 H); 7.32–7.60 (*AB*, *q*, 4 H); 5.35 (*d*, *J* = 3.0, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 158.96; 151.74; 141.81; 138.82; 132.24; 129.03; 128.44; 128.24; 110.22; 51.60. Anal. calc. for $C_{12}H_9ClN_4O_2$ (276.68): C 52.09, H 3.28, N 20.25; found: C 52.31, H 3.26, N 20.33.

*4-(4-Bromophenyl)-4,6-dihydropyrimido[4,5-*d*]pyridazine-2,5-(1*H*,3*H*)-dione* (**4c**): M.p. 361° (MeOH). IR (KBr): 3323 (br.), 1692, 1642, 1252. ^{1}H-NMR (500 MHz, $CDCl_3$): 12.76 (*s*, 1 H); 9.81 (*s*, 1 H); 7.88 (*s*, 1 H); 7.62 (*s*, 1 H); 7.55 (*d*, *J* = 8.3, 2 H); 7.29 (*d*, *J* = 8.3, 2 H); 5.35 (*d*, *J* = 2.5, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 159.00; 151.78; 142.25; 138.87; 131.43; 129.09; 128.65; 120.85; 110.23; 51.71. LC/MS: 323 and 325 ($[M+1]^+$) in the ratio 1:2. Anal. calc. for $C_{12}H_9BrN_4O_2$ (321.13): C 44.88, H 2.82, N 17.45; found: C 45.02, H 2.91, N 17.38.

*4,6-Dihydro-4-(4-methylphenyl)pyrimido[4,5-*d*]pyridazine-2,5-(1*H*,3*H*)-dione* (**4d**). M.p. 352° (MeOH). IR (KBr): 3341 (br.), 1678, 1651. ^{1}H-NMR (500 MHz, $CDCl_3$): 12.70 (*s*, 1 H); 9.73 (*s*, 1 H); 7.79 (*s*, 1 H); 7.61 (*s*, 1 H); 7.13–7.21 (*AB*, *q*, 4 H); 5.30 (*d*, *J* = 3.0, 1 H); 2.27 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 159.00; 151.98; 140.01; 138.65; 136.88; 129.00; 128.94; 126.16; 110.94; 51.75; 20.60. LC/MS: 257 ($[M+1]^+$). Anal. calc. for $C_{13}H_{12}N_4O_2$ (256.26): C 60.93, H 4.72, N 21.86; found: C 60.50, H 4.76, N 22.03.

*4,6-Dihydro-4-(4-methoxyphenyl)pyrimido[4,5-*d*]pyridazine-2,5-(1*H*,3*H*)-dione* (**4e**). M.p. 336° (MeOH). IR (KBr): 3231 (br.), 1673, 1661. ^{1}H-NMR (500 MHz, $CDCl_3$): 12.70 (*s*, 1 H); 9.73 (*s*, 1 H); 7.79 (*s*, 1 H); 7.61 (*s*, 1 H); 7.23 (*d*, *J* = 8.7, 2 H); 6.90 (*d*, *J* = 8.7, 2 H); 5.29 (*d*, *J* = 2.8, 1 H); 3.73 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 158.96; 151.74; 138.69; 136.60; 130.72; 129.06; 126.81; 112.70; 110.32; 56.26; 51.08. LC/MS: 273 ($[M+1]^+$). Anal. calc. for $C_{13}H_{12}N_4O_3$ (272.26): C 57.35, H 4.44, N 20.58; found: C 57.55, H 4.48, N 20.43.

Ethyl 4-(4-Bromophenyl)-6-formyl-1,2,3,4-tetrahydro-2-oxopyrimidine-5-carboxylate (**3c**). To a soln. of **2c** (0.5 mmol) in MeOH, a cold aq. MeOH soln. of AcOAg (0.5 mmol) was added and the mixture stirred for 20 min. Then, the MeOH was evaporated; the mixture diluted with H_2O (20 ml) and then extracted with AcOEt, the extract concentrated, and the residue recrystallized from $CHCl_3$/MeOH: **3c** (63%). Colorless solid. M.p 148°. IR (KBr): 3411, 1717, 1696, 1644. ^{1}H-NMR (300 MHz, $CDCl_3$): 10.48 (*s*, 1 H); 7.50 (*d*, *J* = 8.1, 2 H); 7.43 (*s*, 1 H); 7.23 (*d*, *J* = 8.1, 2 H); 5.94 (*s*, 1 H); 5.53 (*d*, *J* = 2.7, 1 H); 4.21 (*q*, *J* = 7.0, 2 H); 1.25 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 191.78; 163.00; 151.78; 142.26; 138.87; 131.43; 129.09; 128.85; 108.20; 62.26; 51.72; 14.26. Anal. calc. for $C_{14}H_{13}BrN_2O_4$ (353.17): C 47.61, H 3.71, N 7.93; found: C 47.50, H 3.74, N 8.01.

Ethyl 1,2,3,4-Tetrahydro-2-oxo-4-phenyl-6-[(2-phenylhydrazinylidene)methyl]pyrimidine-5-carboxylate (**7**). As described above for **4** (*General Procedure*), with **2a** and phenylhdrazine in place of $N_2H_4 \cdot H_2O$: **7** (73%) M.p. 328–330°. IR (KBr): 3406 (br.), 3236, 1694, 1629, 1254. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.56 (*s*, 1 H); 8.19 (*s*, 1 H); 7.71 (*s*, 1 H); 7.01–7.30 (*m*, 10 H); 5.41 (*d*, *J* = 2.7, 1 H); 5.28 (*s*, 1 H); 4.52 (*d*, *J* = 7.2, 2 H); 1.12 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 165.07; 151.85; 143.30; 142.66; 140.95; 129.48; 128.83; 128.19; 127.71; 126.70; 121.99; 113.40; 102.69; 60.52; 56.13; 14.11. Anal. calc. for $C_{20}H_{20}N_4O_3$ (364.40): C 65.92, H 5.53, N 15.38; found: C 66.05, H 5.49, N 15.44.

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Received February 20, 2012