

A Novel Approach for the Synthesis of Furopyrimidine and Oxobenzofuran Derivatives

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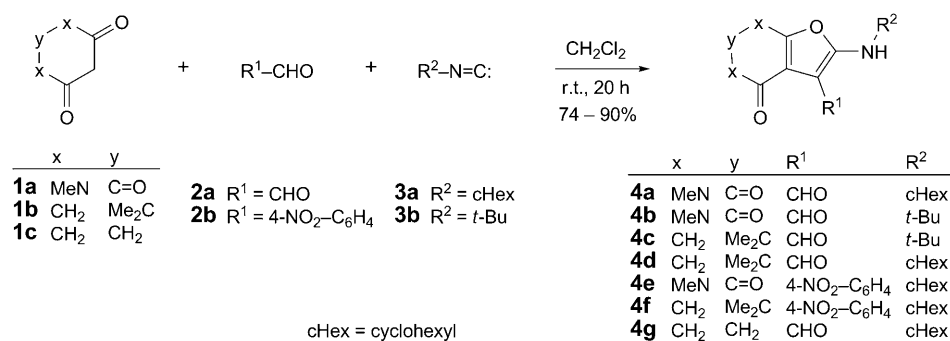
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A novel, efficient one-pot approach for the synthesis of furopyrimidine and oxobenzofuran derivatives **4** by a multicomponent reaction of an isocyanide, an aldehyde, and a CH-acid compound in CH₂Cl₂ is reported (*Scheme 1* and *Table*). The reactions were completed after 20 h at room temperature. This method has the advantages of high yields, simple methodology, and easy workup.

Introduction. – The synthetic routes to furopyrimidine and oxobenzofuran derivatives is not large, and only few procedures have been reported for the synthesis of furopyrimidines [1–4], mostly relying on multi-step reactions giving low yields [1–3]. These compounds are an important structural unit in natural products and are intermediates in drugs and organic synthesis [5][6]. As part of our continuing interest in the development of new synthetic methods in heterocyclic chemistry and the recent interest in isocyanide-based multicomponent reactions [7–10], we now describe an efficient synthesis of furopyrimidine and oxobenzofuran derivatives *via* the reaction of CH-acids with aldehydes and isocyanides in CH₂Cl₂ at room temperature.

Results and Discussion. – The reaction of an aldehyde **2**, an isocyanide **3**, and a CH-acid compound **1** produces a fused furan **4**. The products **4** are derivatives of dioxofuropyrimidines and 2-amino-oxobenzofuranes (*Scheme 1*). Cyclohexyl and *tert*-butyl isocyanide were used as isocyanide **3**, dimedone (= 5,5-dimethylcyclohexane-1,3-

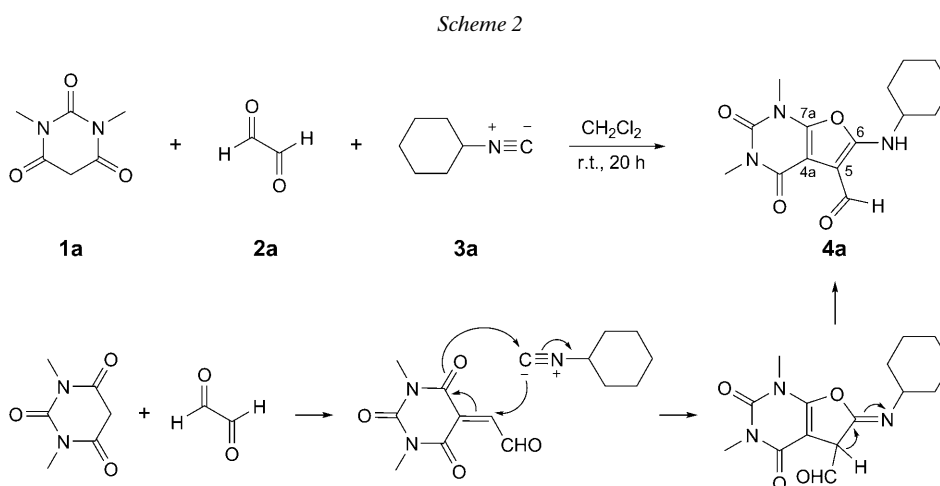
Scheme 1



dione), *N,N'*-dimethylbarbituric acid (=1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione), and cyclohexane-1,3-dione as the CH-acid **1**, and 4-nitrobenzaldehyde and glyoxal (= ethanedial) as the aldehyde **2**. Substrates and products are given in the *Table*. The structures of the products **4a–4g** were deduced from their elemental analyses, and IR and ¹H- and ¹³C-NMR spectra. The mass spectra of **4a–4g** displayed the molecular-ion peak at appropriate *m/z* values. Initial fragmentations involved the loss of alkylamino moieties and scission of the heterocycle moieties.

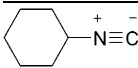
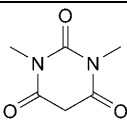

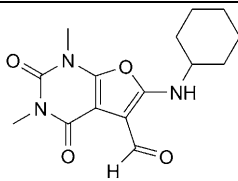
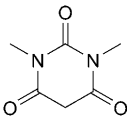

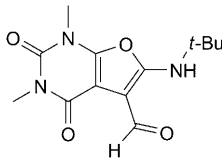
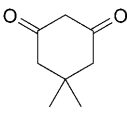

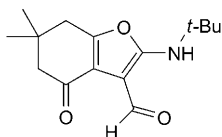
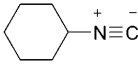
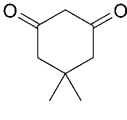

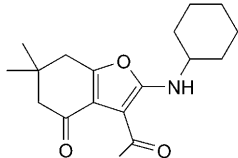
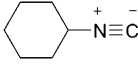
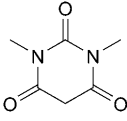
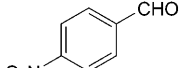
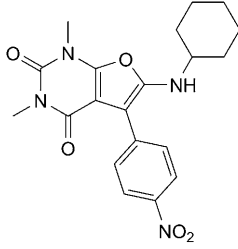
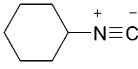
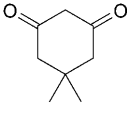
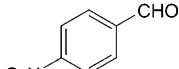
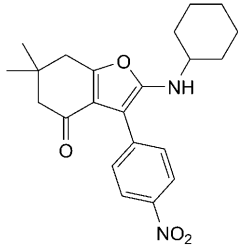
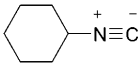
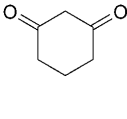

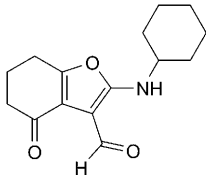
The ¹H-NMR spectrum of **4a** consisted of a *m* for the cyclohexyl substituent ($\delta(\text{H})$ 1.27–2.03) and of two single sharp *s* for Me groups ($\delta(\text{H})$ 3.41 and 3.54). A *m* was observed for the N–CH group ($\delta(\text{H})$ 3.69), a broad signal for the NH group ($\delta(\text{H})$ 7.88), and a *s* for the CHO group ($\delta(\text{H})$ 9.82), in agreement with the suggested structure. The ¹H-decoupled ¹³C-NMR spectrum of **4a** showed 13 sharp signals in agreement with the proposed structure. The characteristic signal of the CHO C-atom was discernible ($\delta(\text{C})$ 183.25), as well as the four signals ($\delta(\text{C})$ 94.17, 97.59, 148.11, and 150.09) for four C-atoms of the furan moiety. Partial assignments of these resonances are given in the *Exper. Part*.

A mechanism for the synthesis of **4a** is proposed in *Scheme 2*. The formation of the fused structure can be rationalized by initial formation of a conjugated electron-deficient heterodiene by *Knoevenagel* condensation of aldehyde **2a** and CH-acid **1a**, followed by a [1 + 4] cycloaddition reaction or a *Michael*-type addition reaction with isocyanide **3a** to afford an iminofuran derivative, which was then isomerized to product **4**.



In conclusion, we have described a new, general, and successful strategy for the convenient synthesis of furopyrimidine and oxobenzofuran derivatives. These new one-pot reactions were performed in CH_2Cl_2 at room temperature under neutral conditions and in the absence of any catalyst, the substrates being mixed without any prior activation or modification. The advantages of the present procedure are experimental simplicity, easy workup, and high yields (> 70%) of products.

Table. Synthesis of Furopyrimidine and Oxobenzofuran Derivatives

R-NC 3	CH-Acid 1	Aldehyde 2	Product 4
			 4a
$t\text{-Bu-N}\equiv\text{C}^-$			 4b
$t\text{-Bu-N}\equiv\text{C}^-$			 4c
			 4d
			 4e
			 4f
			 4g

Experimental Part

General. Glyoxal, *N,N'*-dimethylbarbituric acid, alkyl isocyanides, and other reagents and solvents used in this work were obtained from *Fluka* (Buchs, Switzerland) and used without further purification. M.p.: *Gallenkamp* electrothermal 9100 apparatus; uncorrected. IR Spectra: *Bruker-Tensor-27* spectrometer; KBr pellets; $\tilde{\nu}$ in cm^{-1} . ^1H - and ^{13}C -NMR Spectra: *Bruker-DRX-300-Avance* instrument; CDCl_3 as solvent; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Shimadzu-QP-GC-Mass-1100-EX* spectrometer operating at an ionization potential of 70 eV; in m/z (rel. %). Elemental analyses: *Heraeus-CHN-O-Rapid* analyzer; exper. values in agreement with calc. values.

General Procedure, Exemplified for 4a. A mixture of glyoxal (**2a**; 0.058 g, 1 mmol) and cyclohexyl isocyanide (**3a**; 0.111 g, 1 mmol) in CH_2Cl_2 (8 ml) was stirred at r.t. Then, a soln. of *N,N'*-dimethylbarbituric acid (**1a**; 0.156 g, 1 mmol) in CH_2Cl_2 (2 ml) was added to the mixture during 10 min. The mixture was stirred for 20 h at r.t. (TLC monitoring). After completion of the reaction, the solvent was evaporated and the residue purified by column chromatography (silica gel 60 (70–230 mesh; *Merck*), hexane/AcOEt 4:1): product **4a**.

6-(Cyclohexylamino)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxofuro[2,3-d]pyrimidine-5-carboxaldehyde (**4a**): Yield 0.259 g (85%). Pale yellow crystals. M.p. 197–199°. IR: 3320 (N–H), 1685 and 1577 (C=O), 1048 (C–N). ^1H -NMR: 1.27–2.03 (*m*, 10 H of cHex); 3.41 (*s*, MeN); 3.54 (*s*, MeN); 3.66–3.71 (*br. m*, CH–N); 7.88 (*br. s*, NH); 9.82 (*s*, CHO). ^{13}C -NMR: 24.43, 25.12, 28.38 (5 C of cHex); 29.73, 33.38 (2 MeN); 52.14 (CHNH); 94.17 (C(4a)); 97.59 (C(5)); 148.11 (C(6)); 150.09 (C(7a)); 157.13, 159.16 (2 C=O); 183.25 (CHO). EI-MS: 305 (23, M^+), 223 (100), 166 (37), 138 (29), 83 (31), 55 (51). Anal. calc. for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_4$ (305.33): C 59.01, H 6.27, N 13.76; found: C 58.9, H 6.3, N 13.7.

6-(*tert*-Butylamino)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxofuro[2,3-d]pyrimidine-5-carboxaldehyde (**4b**): Yield 0.223 g (80%). Orange solid. M.p. 135–137°. IR: 3323 (N–H), 2973 (C–H), 1681, 1575 (C=O), 1038 (C–N). ^1H -NMR: 1.46 (*s*, *t*-Bu); 3.36 (*s*, MeN); 3.52 (*s*, MeN); 8.12 (*br. s*, NH); 9.77 (*s*, CHO). ^{13}C -NMR: 28.07, 29.73 (2 MeN); 29.88 (Me_3C); 53.84 (Me_3C); 93.74 (C(4a)); 94.85 (C(5)); 148.37 (C(6)); 150.01 (C(7a)); 157.67, 159.40 (2 C=O); 183.17 (CHO). EI-MS: 279 (21, M^+), 222 (100), 106 (61), 137 (70), 119 (19), 109 (29), 57 (60). Anal. calc. for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_4$ (279.29): C 55.91, H 6.14, N 15.05; found: C 56.1, H 6.2, N 15.1.

2-(*tert*-Butylamino)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxobenzofuran-3-carboxaldehyde (**4c**): Yield 0.195 g (74%). Orange oil. IR: 3300 (N–H), 2962 (C–H), 1650, 1575 (C=O), 1014 (C–N). ^1H -NMR: 1.45 (*s*, *t*-Bu); 2.37 (*s*, CH_2); 2.67 (*s*, CH_2); 8.17 (*br. s*, NH); 9.84 (*s*, CHO). ^{13}C -NMR: 28.70, 28.53 (2 Me); 29.73 (Me_2C); 35.44 (Me_2C); 35.44, 36.73 (2 CH_2); 53.12 (Me_2C); 95.28, 99.10, 157.47, 162.94 (furan ring); 183.25 (CHO); 193.90 (C=O). EI-MS: 263 (21, M^+), 247 (31), 206 (100), 192 (17), 150 (37), 123 (37), 95 (20), 83 (24), 57 (98). Anal. calc. for $\text{C}_{15}\text{H}_{12}\text{NO}_3$ (263.33): C 68.42, H 8.04, N 5.32; found: C 68.4, H 8.1, N 5.2.

2-(Cyclohexylamino)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxobenzofuran-3-carboxaldehyde (**4d**): Yield 0.260 g (90%). Orange solid. M.p. 126–128°. IR: 3247 (N–H), 2924 (C–H), 1656, 1588 (C=O), 1077 (C–N). ^1H -NMR: 1.20–1.93 (*m*, 10 H of cHex); 2.41 (*s*, CH_2); 2.68 (*s*, CH_2); 3.71 (*br. s*, CHN); 7.8 (*br. s*, NH); 9.88 (*s*, CHO). ^{13}C -NMR: 24.59, 25.23, 33.40 (5 C of cHex); 28.50, 28.67 (2 Me); 35.42 (Me_2C); 35.45, 36.70 (2 CH_2); 57.21 (CHNH); 93.01, 98.50, 157.51, 161.50 (furan ring); 183.72 (CHO); 196.50 (C=O). EI-MS: 289 (24, M^+), 207 (73), 12 (26), 151 (96), 122 (100), 95 (27), 83 (29), 55 (47). Anal. calc. for $\text{C}_{17}\text{H}_{23}\text{NO}_3$ (289.37): C 70.56, H 8.01, N 4.84; found: C 70.6, H 7.9, N 4.8.

6-(Cyclohexylamino)-1,3-dimethyl-5-(4-nitrophenyl)furo[2,3-d]pyrimidine-2,4(1H,3H)-dione (**4e**): Yield 0.310 g (78%). Orange solid. M.p. 108–110°. IR: 3300 (N–H), 1673 (C=O), 1521, 1347 (NO_2), 1110 (C–O). ^1H -NMR: 1.24–1.78 (*m*, 10 H of cHex); 3.37 (*s*, MeN); 3.48 (*s*, MeN); 3.72–3.79 (*br. m*, CHN); 6.32 (*br. s*, NH); 7.65 (*d*, $^3J = 8.7$, 2 arom. H); 7.91 (*d*, $^3J = 8.7$, 2 arom. H). ^{13}C -NMR: 24.77, 25.32, 28.38 (5 C of cHex); 28.24, 29.52 (2 MeN); 57.19 (CHNH); 94.57 (C(4a)); 101.35 (C(5)); 123.47, 129.48, 138.10, 145.87 (arom. C); 148.64 (C(6)); 150.30 (C(7a)); 160.55, 162.02 (2 C=O). EI-MS: 398 (10, M^+), 304 (19), 277 (10), 151 (50), 126 (24), 83 (100), 55 (34). Anal. calc. for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_5$ (398.41): C 60.29, H 5.57, N 14.06; found: C 60.3, H 5.6, N 14.1.

2-(Cyclohexylamino)-6,7-dihydro-6,6-dimethyl-3-(4-nitrophenyl)benzofuran-4(5H)-one (**4f**): Yield 0.313 g (82%). Pale yellow oil. IR: 3400 (N–H), 1672, 1597 (C=O), 1522, 1346 (NO_2), 1108 (C–O).

¹H-NMR (500 MHz): 1.13–1.75 (*m*, 10 H of cHex); 2.61 (*s*, CH₂); 2.75 (*s*, CH₂); 3.81–3.90 (*br. m*, CHN), 5.62 (*d*, ³*J* = 8.1, NH); 7.60 (*d*, ³*J* = 8.0, 2 arom. H); 8.25 (*d*, ³*J* = 8.0, 2 arom. H). ¹³C-NMR: 24.71, 25.34, 32.64 (5 C of cHex); 27.45, 29.26 (2 Me); 31.48 (Me₂C); 35.45, 36.75 (2 CH₂); 56.06 (CHNH); 92.50, 98.15, 156.95, 160.50 (furan ring); 123.44, 132.36, 137.80, 146.10 (arom. C); 186.47 (CHO); 193.85 (C=O). EI-MS: 382 (13, *M*⁺), 324 (12), 299 (24), 283 (45), 167 (30), 150 (46), 128 (31), 104 (19), 83 (100), 55 (67). Anal. calc. for C₂₂H₂₆N₂O₄ (382.45): C 69.09, H 6.85, N 7.32; found: C 69.1, H 6.8, N 7.4.

2-(Cyclohexylamino)-4,5,6,7-tetrahydro-4-oxobenzofuran-3-carboxaldehyde (**4g**): Yield 0.195 g (75%). Yellow oil. IR: 3242 (N–H), 2930 (C–H), 1660, 1592 (C=O). ¹H-NMR (500 MHz): 1.09–2.05 (*m*, 10 H of cHex); 2.16–2.25 (*m*, CH₂CH₂CO); 2.43–2.51 (*m*, CH₂C=C); 2.78 (*AB q*, CH₂CH₂CO); 3.69–3.77 (*m*, CHN), 7.82 (*br. s*, NH); 9.85 (*s*, CHO). ¹³C-NMR: 24.59, 25.23, 33.40 (5 C of cHex); 25.50, 35.45, 36.70 (3 CH₂); 56.85 (CHNH); 93.58, 99.10, 157.25, 162.48 (furan ring); 183.41 (CHO); 193.68 (C=O). EI-MS: 261 (16, *M*⁺), 178 (60), 163 (27), 150 (100), 121 (95), 98 (24), 83 (30). Anal. calc. for C₁₅H₁₉NO₃ (261.32): C 68.94, H 7.33, N 5.36; found: C 68.9, H 7.3, N 5.4.

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