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Regioselective synthesis of the 3,4-dihydrofuro[3,2-*d*]pyrimidin-2(1*H*)-one skeleton: a new class of compound

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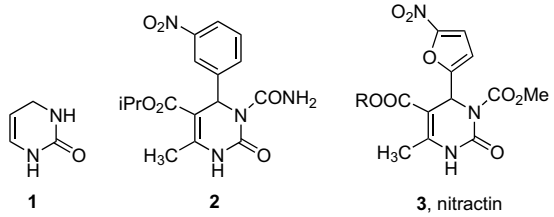
ABSTRACT

We hereby report the first preparation of the 3,4-dihydrofuro[3,2-*d*]pyrimidin-2(1*H*)-one skeleton formed by two controlled Curtius rearrangements of the corresponding acyl azides, prepared from 2-(2-methoxy-2-oxoethyl)furan-3-carboxylate via the hydrazide. Rearrangement of the acyl azides followed by trapping by nucleophiles and intramolecular trapping provided the target compounds.

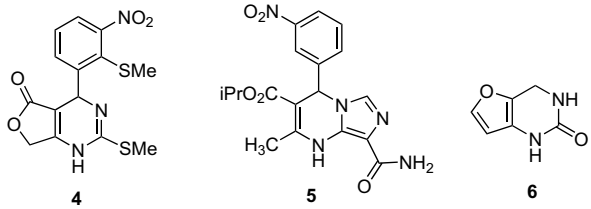
1. Introduction

The Italian chemist Biginelli reported for the first time in 1893 the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPM) of type **1** by a multiple-component chemical reaction starting from ethylacetoacetate, aryl aldehyde and urea.[1–4] Over the last two decades, interest in dihydropyrimidones has increased dramatically.[5]



DHPMs and their derivatives show a wide scope of important pharmacological properties, such as calcium channel modulation, antihypertensive activity, and α_{1a}-antagonists.[6,7] However, most did not show significant antihypertensive activity. Modification of the substituent at N3 led to the development of orally long-lasting antihypertensive compounds such as **2** and its derivatives.[8] Furthermore, it has been established that the absolute stereochemistry at the C4 carbon atom is very important. For example, the desired antihypertensive effect was observed only with the (*R*)-enantiomer of **2**.[6–8] Nitrofuryl-substituted DHPM derivative, nitractin **3**[9] displayed activity against viruses of the trachoma group and modest antibacterial activity.[10,11] Besides the monocyclic DHMP derivatives, some fused analogs, which incorporate hetero- or carbocyclic rings attached to either C2/N3 or the C5/C6 positions of dihydropyrimidine such as **4**[12] and **5**[13] also possess calcium channel blocking activity.

Recently, several isolated marine alkaloids with interesting biological activities were found to contain the dihydropyrimidinone-5-carboxylate skeleton.[14,15]



The Biginelli reaction is not applicable to the synthesis of a C5/C6 fused system, therefore, an efficient method for the preparation of the fused analogs at the C5/C6 position of DHPMs is highly desirable. In this paper we describe a new method for the synthesis of

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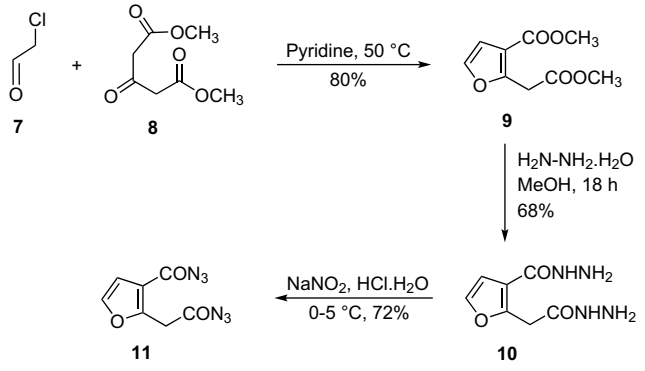
the 3,4-dihydrofuro[3,2-*d*]pyrimidin-2(1*H*)-one skeleton **6** and some derivatives.

2. Results and discussion

The synthesis of the key compound **11** used in the synthesis of DHMPs began with the readily available chloroacetaldehyde **7** and dimethyl acetonedicarboxylate **8** followed by the sequence of steps outlined in Scheme 1.

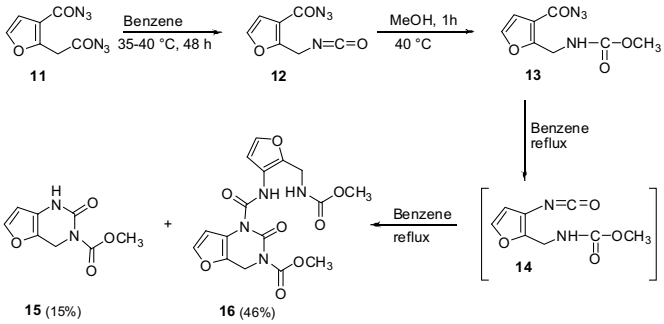


Scheme 1. Synthesis of the key compound, diazide **11**.

Treatment of dimethyl acetonedicarboxylate **8** with chloroacetaldehyde **7** in the presence of pyridine yielded the diester **9** in 80% yield.[16] The diester was successfully converted to the desired dihydrazide **10** by treatment of **9** with hydrazine in methanol. The resulting compound was reacted at low temperature with $NaNO_2$ and HCl to give the corresponding diazide **11** (Scheme 1).

After successful synthesis of diacyl diazide **11** we turned our attention to the Curtius rearrangement. Our plan for the construction of the desired heterocyclic ring system involved an intramolecular cyclization reaction of the diisocyanate, which can be generated by the Curtius reaction.[17–19] Compound **11** contains two different acyl azide functionalities, with one of the carbonyl groups conjugated with the furan ring while the other one is not.

We noticed that the stability of those acyl azides is different, with the conjugated one more stable than the other one. Thus, diacyl diazide **11** was allowed to heat in benzene at 35–40 °C for 48 h to effect the transformation of the alkyl acyl azide functionality to the corresponding monoisocyanate **12** (Scheme 2). Treatment of the formed isocyanate **12** in benzene with MeOH at 40 °C for 1 h gave the urethane **13** in 70% yield. The urethane **13** containing an acyl azide functionality was again subjected to Curtius rearrangement by heating at reflux for 30 h in benzene under nitrogen atmosphere to effect its quantitative transformation. The expected intramolecular cyclization product **15** was unfortunately only formed in 15%. The major product **16** (46%) was formed by the addition of the NH in **15** to



Scheme 2. Curtius rearrangement of diazide **11**.

the initially formed isocyanate **14**. COSY, HMQC, and HMBC experiments allowed the assignment of the structure **16**. Finally X-ray diffraction analysis of **16** was carried out. The results of this study confirmed unambiguously the proposed structure (Fig. 1).

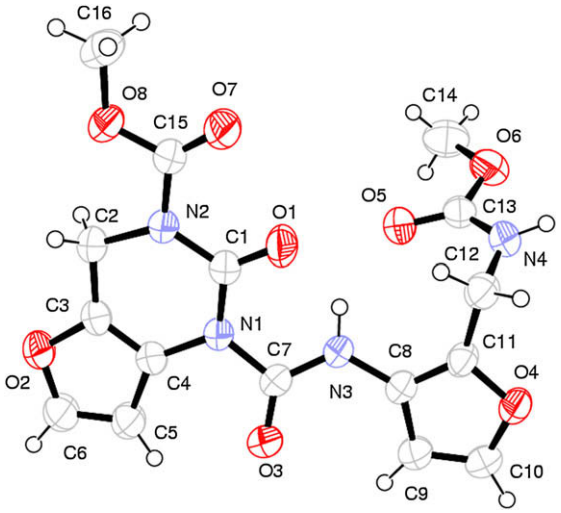
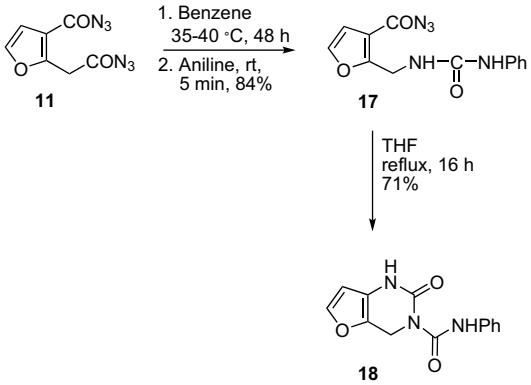


Figure 1. Thermal ellipsoid drawing of compoud **16**.

In order to hinder the intermolecular addition reaction between **15** and **14**, we decided to increase the nucleophilicity of the NH group in **14** and force the system to undergo intramolecular cyclization. For this reason, isocyanate **12** generated at 35–40 °C in benzene, was trapped with aniline to give **17** in 84% yield. Curtius rearrangement of the acyl azide **17**, carried out in dry tetrahydrofuran at reflux for 16 h afforded the pyrimidinone derivative **18** in 71% yield (Scheme 3). The structure of **18** has been fully characterized.



Scheme 3. Curtius rearrangement of **17** and intramolecular cyclization.

3. Conclusion

In conclusion, 3,4-dihydrofuro[3,2-*d*]pyrimidin-2(1*H*)-one (**6**), a new heterocyclic system has been prepared starting from methyl 2-(2-methoxy-2-oxoethyl)furan-3- carboxylate (**9**), by a 6 step procedure, including two controlled Curtius rearrangements of the corresponding acyl azides **11** and **17**. Considering the multitude of choices in nucleophile selection, we are confident that this approach can be extended to a variety of novel furo-condensed new heterocyclic systems. Efforts to elucidate the versatility of **11** reported herein in expanded structures, and applications to generate furo-condensed seven-membered rings are currently underway in our laboratories.

4. Experimental section

4.1. General

Melting points are uncorrected. Infrared spectra were obtained from solution in 0.1 mm cells or KBr pellets on an FT-IR Bruker Vertex 70 instrument. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-Biospin (DPX-400) instrument. Apparent splitting is given in all cases. Column chromatography was performed on silica gel (60-mesh, Merck), TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminum plates.

4.2. 2-(2-Hydrazino-2-oxoethyl)-3-furohydrazide (10)

Hydrazine monohydrate (9.8 mL, 202 mmol) was added to a stirred solution of diester **9** (10 g, 50.5 mmol) in methanol (150 mL) and heated at reflux for 18 h. The solvent was evaporated and the crude product was purified by washing with a mixture of methanol/ethyl acetate (2:1) to give dihydrazide **10** as a white solid (6.8 g, 68%), mp 152–153 °C. [Found: C, 42.22; H, 5.03; N, 28.10. $C_7H_{10}N_4O_3$ requires C, 42.42; H, 5.09; N, 28.27%.] ν_{max}(KBr) 3309, 3009, 1687, 1626, 1515, 1418, 1350, 1238, 1016, 730 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 9.59 (1H, br s, N*H*), 9.24 (1H, br s, –N*H*), 7.56 (1H, d, *J* 1.9 Hz,=C*H*), 6.82 (1H, d, *J* 1.9 Hz,=C*H*), 4.33 (4H, br s, –NH_2) 3.82 (2H, s, –CH_2); δ_C (100.6 MHz, DMSO-d_6) 167.3, 162.4, 152.3, 141.6, 116.2, 109.0, 32.7.

4.3. Synthesis of 2-(2-azido-2-oxoethyl)-3-furoyl azide (11)

Dihydrazide **10** (3 g, 15.15 mmol) was dissolved in aq solution of HCl (70 mL, 1 M) and cooled to 0 °C. To this, a solution of sodium nitrite (2.1 g, 30.3 mmol) in water (40 mL) was added dropwise at 0–5 °C and stirred at this temperature range for 30 min. The mixture was extracted with diethyl ether (2×70 mL). The combined organic phases were washed with satd aq Na_2CO_3 solution (50 mL) and then brine (40 mL), dried over $MgSO_4$ and the solvent was evaporated to give diacyl azide **11** as a colorless oil (2.4 g, 72%); ν_{max}(KBr) 2926, 2144, 1687, 1600, 1517, 1420, 1300, 1187, 1071 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 7.30 (1H, d, *J* 2.0 Hz,=C*H*), 6.63 (1H, d, *J* 2.0 Hz,=C*H*), 4.05 (2H, s, –CH_2); δ_C (100.6 MHz, $CDCl_3$) 174.9, 168.2, 154.2, 142.6, 117.5, 110.6, 35.9.

4.4. 2-(Isocyanatomethyl)-3-furoyl azide (12)

The diacyl azide **11** (2.8 g, 12.7 mmol) was dissolved in dry benzene (100 mL) and stirred at 37–42 °C for 48 h. The solvent was evaporated to give a colorless oil of **12** was analyzed by NMR spectroscopy indicating the formation of half-isocyanate in 85% yield; ν_{max}(KBr) 3162, 3134, 2257, 2137, 1688, 1599, 1516, 1404, 1341, 1302, 1262, 1184, 1129, 1049, 913 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40 (1H, d, *J* 2.0 Hz,=C*H*), 6.70 (1H, d, *J* 2.0 Hz,=C*H*), 4.78 (2H, s, –CH_2); δ_C (100.6 MHz, $CDCl_3$) 167.5, 156.0, 142.3, 124.9, 115.9, 111.4, 38.4.

4.5. Methyl (3-(azidocarbonyl)furan-2-yl)methyl-carbamate (13)

Excess methanol (5 mL) was added to a stirred solution of the half-isocyanate **12** (2.1 g, 10.9 mmol) in dry benzene (50 mL) and stirred at 40 °C for 1 h. The solvent was evaporated to give the crude product, which was then purified and separated by column chromatography eluting with dichloromethane/hexane/ethyl acetate (1:1:1) to give urethane **13** as a white solid (1.72 g, 70%), mp 95–96 °C. [Found: C, 43.07; H, 3.65; N, 24.95. $C_8H_8N_4O_4$ requires C, 42.86; H, 3.60; N, 24.99%.] ν_{max}(KBr) 3334, 3129, 2944, 2159, 1715, 1671, 1518, 1446, 1256, 1070 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (1H, d, *J* 2.0 Hz,=C*H*), 6.58 (1H, d, *J* 2.0 Hz,=C*H*), 5.40 (1H, br s, –N*H*), 4.61 (2H, d, *J* 6.2 Hz, –CH_2), 3.62 (3H, s, –OCH_3); δ_C (100.6 MHz, $CDCl_3$) 168.5, 159.4, 156.9, 141.9, 116.0, 110.5, 52.4, 37.6.

4.6. Thermolysis of 13

The acyl azide **13** (0.3 g, 3.35 mmol) was dissolved in dry benzene (10 mL) and heated at reflux for 30 h. The solvent was evaporated and the crude product was purified and separated by column chromatography eluting with ethyl acetate/dichloromethane (2:1) to give cyclic compound **15** and **16**.

*4.6.1. Methyl 2-oxo-1,4-dihydrofuro[3,2-d]pyrimidine-3(2H)-carboxylate (**15**)*

White solid, 40 mg, 15%, mp 152–153 °C. [Found: C, 49.11; H, 4.05; N, 14.43. $C_8H_8N_2O_4$ requires C, 48.98; H, 4.11; N, 14.28%.] ν_{max}(KBr) 3428, 1772, 1719, 1708, 1540, 1524, 1437, 1366, 1291, 1273, 1219, 1121 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40 (1H, br s, –N*H*), 7.24 (1H, dt, *J* 2.0, 1.0 Hz,=C*H*), 6.20 (1H, d, *J* 2.0 Hz,=C*H*), 4.90 (2H, d, *J* 1.0 Hz, –CH_2), 3.91 (3H, s, –OCH_3); δ_C (100.6 MHz, $CDCl_3$) 154.1, 149.7, 141.9, 130.1, 120.6, 101.5, 53.7, 44.1.

*4.6.2. Methyl 1-[{2-[(methoxycarbonyl)amino]methyl-3-furylamino}carbonyl]-2-oxo-1,4-dihydrofuro[3,2-d]pyrimidine-3(2H)-carboxylate (**16**)*

White solid from ethyl acetate, 120 mg, 46%, mp 163–164 °C. [Found: C, 48.90; H, 4.11; N, 14.25. $C_{16}H_{16}N_4O_8$ requires C, 48.98; H, 4.11; N, 14.28%.] ν_{max}(KBr) 3358, 3139, 2964, 1780, 1710, 1640, 1531, 1448, 1396, 1266, 1130, 1080, 765 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.49 (1H, br s, –N*H*), 7.31 (1H, d, *J* 2.0 Hz,=C*H*), 7.30 (1H, d, *J* 2.0 Hz,=C*H*), 6.92 (1H, d, *J* 2.0 Hz,=C*H*), 6.62 (1H, br s,=C*H*), 5.34 (1H, br s, –N*H*), 4.87 (2H, s, –CH_2), 4.34 (2H, d, *J* 6.0 Hz, –CH_2), 3.94 (3H, s, –OCH_3), 3.68 (3H, s, –OCH_3); δ_C (100.6 MHz, $CDCl_3$) 157.4, 154.2, 152.3, 150.6, 142.3, 142.2, 141.6, 134.1, 121.6, 120.8, 108.9, 108.0, 55.1, 52.6, 44.5, 36.4.

4.7. 2-{[(Anilinocarbonyl)amino]methyl}-3-furoyl azide (17)

Aniline (0.94 mL, 10.4 mmol) was added to a stirred solution of the half-isocyanate **12** (1.8 g, 8.7 mmol, synthesized as described above) in dry benzene (80 mL) and stirred at room temperature for 5 min. The precipitate was filtered and washed with benzene (50 mL) and purified by column chromatography eluting with ethyl acetate/hexane (2:1) to give urethane **17** as a white solid from ethyl acetate (2.1 g, 84%), mp 141–142 °C. [Found: C, 54.30; H, 3.79; N, 24.33. $C_{13}H_{11}N_5O_3$ requires C, 54.74; H, 3.89; N, 24.55%.] ν_{max}(KBr) 3326, 2153, 2128, 1689, 1638, 1596, 1570, 1444, 1306, 1263, 1184, 1052, 951 cm^{-1}; δ_H (400 MHz, acetone-d_6) 8.00 (1H, br s, –N*H*), 7.44 (1H, d, $J_{5,4}$=2.0 Hz,=C*H*), 7.35 (2H, br d, *J* 7.6 Hz,=C*H*), 7.10 (2H, br t, *J* 8.2 Hz,=C*H*), 6.79 (1H, tt, *J* 7.4, 1.0 Hz,=C*H*), 6.56 (1H, d, *J* 2.0 Hz,=C*H*), 6.19 (1H, br t, *J* 6.0 –N*H*), 4.62 (2H, d, *J* 6.0 Hz, –CH_2); δ_C (100 MHz, acetone-d_6) 168.9, 161.9, 155.8, 143.2, 141.4, 129.5, 122.5, 119.0, 116.1, 111.2, 37.1.

4.8. 2-Oxo-*N*-phenyl-1,4-dihydrofuro[3,2-*d*]pyrimidine-3(2*H*)-carboxamide (18)

The acyl azide **17** (0.8 g, 2.81 mmol) was dissolved in dry THF (60 mL) and heated at reflux for 16 h. The solvent was evaporated and the crude product was purified by column chromatography using silica gel (50 g) eluting with ethyl acetate/dichloromethane (1:1) to give cyclic compound **18** as a white solid from ethyl acetate (0.51 g, 71%), mp 203–205 °C. [Found: C, 61.11; H, 4.60; N, 16.12. $C_{13}H_{11}N_3O_3$ requires C, 60.70; H, 4.31; N, 16.33%.] ν_{max}(KBr) 3413, 3202, 3142, 1719, 1655, 1595, 1558, 1438, 1205, 1161, 1025, 747 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.42 (1H, br s, –NH), 7.46 (2H, br d, *J* 7.6 Hz,=C*H*), 7.26 (2H, br t, *J* 7.4 Hz,=C*H*), 7.22 (1H, dt, *J* 2.0,

1.0 Hz,=C*H*), 7.04 (1H, tt, *J* 7.4, 1.0 Hz,=C*H*), 6.51 (1H, br s, –N*H*), 6.10 (1H, d, *J* 2.0 Hz,=C*H*), 4.99 (2H, br s, –CH_2); δ_C (100.6 MHz, $CDCl_3$) 153.9, 152.3, 142.7, 137.8, 130.9, 129.0, 124.1, 120.4, 120.1, 101.4, 43.6.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 719646. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Supplementary data

^{1}H and ^{13}C NMR spectra for all new compounds and crystallographic information file (CIF) for compound **16** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.090.

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