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Facile synthesis of novel 5-amino 1,3-disubstituted tetrahydropyrimidinones

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Dedicated to Professor David E. Cane on the occasion of his 60th birthday

Abstract—The synthesis of novel, 5-amino 1,3-disubstituted tetrahydropyrimidinones, and 5-aminobarbiturates are presented.

Tetrahydropyrimidinones are one of the more common core heterocyclic structures in biologically active molecules.[1] Many of these derivatives, including the selected structures shown in Figure 1, possess a wide range of biological activities.[1]

Syntheses of variously substituted derivatives have been reported.[1,2] Two general synthetic routes include cyclizations of 1,3-diamines with phosgene-type reagents,[1b,c] and 1,3-dihalides with ureas.[3]

In one of our recent drug discovery programs, we were interested in preparing variously substituted 5-amino tetrahydropyrimidinones **4** (Fig. 2). Despite the wide presence of tetrahydropyrimidinones, only one 5-amino tetrahydropyrimidinone structure, a generically claimed selective muscarinic agonist by Merck (**5**, Fig. 2), was reported without synthesis details.[4]

Presumably the synthesis of **4** could be achieved from a recently reported 5-acetoxy tetrahydropyrimidinone intermediate through lengthy reaction sequence.[5] However, from a parallel synthesis requirement, we would preferably like to prepare **4** from a simple starting primary amine **6** bearing easily installable R_1 and R_2 (Fig. 3). After experiencing difficulties in either cyclization of ureas with 1,3-dihalide intermediates or synthesizing possible tri-amine intermediates for cyclization with phosgene or phosgene equivalents, we envisioned that a barbiturate type intermediate **8** could be suitable for nitration at its 5-position to provide the

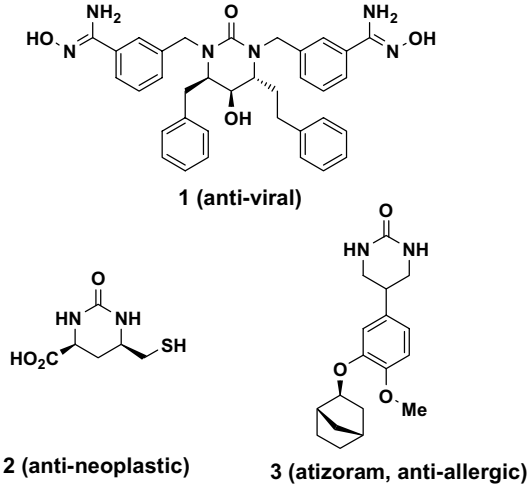

Figure 1. Selected biologically active tetrahydropyrimidinones.

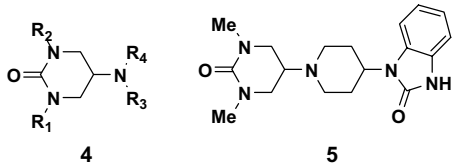

Figure 2. 5-Amino 1,3-disubstituted tetrahydropyrimidinones.

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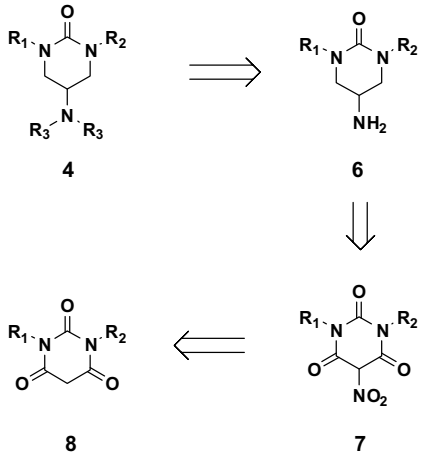
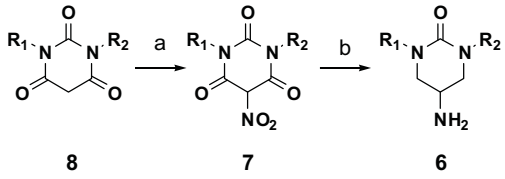


Figure 3. Retrosynthesis plan.

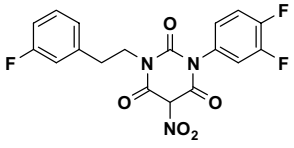
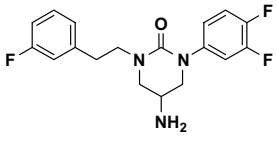
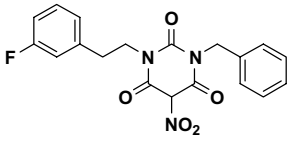
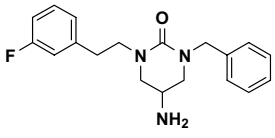
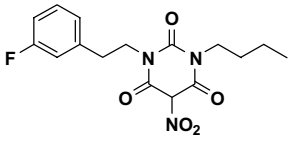
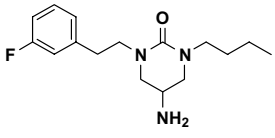
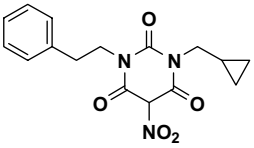
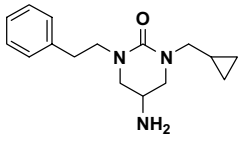
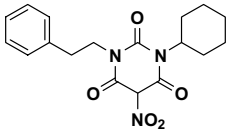
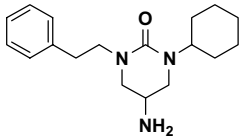
nitrobarbiturate intermediate **7**, which in turn could be reduced to afford the desired structure **6** (Fig. 3). In essence, the incorporation of the two carbonyl groups not only render the introduction of the nitrogen group possible but also facilitate the ring formation reaction.



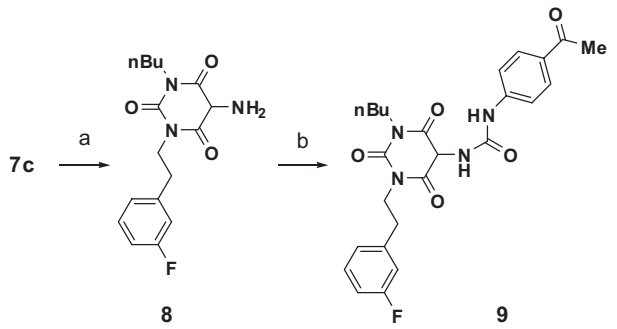
Scheme 1. Reagents and conditions: (a) N_2O_4; (b) $Me_2S{\cdot}BH_3$, THF.

This route indeed proved to be successful. *N*,*N*′-Disubstituted barbiturates **8** were synthesized from symmetric or asymmetric ureas, which are easily prepared from commercially available amines and isocyanates, and malonyl dichloride in good yields as crystalline solids, following a literature described procedure.[6] Mono-nitration of the 5-position by nitric acid was difficult to achieve despite a recent publication.[7] However, by using a solid–gas reaction condition with NO_2 as a nitration source, mono-nitration was exclusively achieved (Scheme 1).[8] The procedure affords the desired solid mono-nitrated product **7** without bis-nitration and avoids any purification procedures (Table 1).[8] While attempted reduction of 5-nitrobarbiturate **7** by $LiAlH_4$ resulted in loss of the nitro group, complete reduction

Table 1. Conversion of barbiturates **8** to 5-aminopyrimidinones **6** via 5-nitrobarbiturates **7**

5-Nitrobarbiturate **7**	Yield[a] (%)	5-Aminopyrimidinone **6**	Yield[b] (%)
 **7a**	96	 **6a**	67
 **7b**	98	 **6b**	59
 **7c**	96	 **6c**	61
 **7d**	90	 **6d**	65
 **7e**	85	 **7e**	52

[a] HPLC yield (±2% with different sampling of the solid).
[b] Isolated yield of pure compound for two steps.



Scheme 2. Reagents and conditions: (a) Raney nickel/H_2, CH_3COOH, MeOH; (b) isocyanate, dichloroethane (47% for two steps).

of **7** to **6** was achieved by treatment with $Me_2S{\cdot}BH_3$.[9] The purified overall yield for two-step sequence is generally over 50% (Table 1).[9] To the best of our knowledge, this is the first report that a none-aromatic nitro group was directly reduced to an amino group solely by the borane reagent. Even though it is not rigorously established, we believe that the neighboring carbonyl groups played a critical role in this nitro group reduction by borane.

Hydrogenation of **7** should afford 5-aminobarbiturate, another medicinally interesting structure, which could not be easily prepared from literature procedures.[10] For example, even though Pd/C catalyzed hydrogenation gave a messy mixture, Raney nickel catalyzed hydrogenation of **7c** afforded a clean conversion to **8**, which was very unstable and reacted with an isocyanate to afford a urea derivative **9** as shown in Scheme 2.[11]

In summary, a very brief and facile synthesis had been achieved for 5-amino 1,3-disubstituted tetrahydropyrimidinones through an interesting solid–gas reaction and a direct borane reduction of one nitro and two amide groups in one pot. However, it should be noted that for asymmetrical ureas this quick synthesis route provides only a racemic mixture. Possible chiral compounds should be accessible through a chiral acetoxy compound.[5]

Acknowledgements

The author is grateful to Dr. Graham S. Poindexter for critically reviewing the manuscript and to Drs. Gene Dubowchik and John Macor for their support and encouragements. Mr. Thomas Klose's extensive literature search on the 5-amino tetrahydropyrimidinone structure and borane reduction of the nitro group is greatly appreciated.

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9. Reduction procedure: To a suspension of **7** (0.5 mmol) in THF (2.5 mL) at rt was added $Me_2S{\cdot}BH_3$ (2.0 mL, 8 equiv, 2.0 M in THF). After stirring at rt for 3 h, the mixture gradually turned to a clear solution and was heated to 70 °C for 8 h (LCMS indicated the complete conversion of the starting material). After the mixture was cooled to rt, 1 mL methanol (caution: gas evolves) followed by 1 mL HCl (5 N) was added to the reaction mixture. The resulted mixture was stirred at rt overnight (14 h) and then basified with NaOH (1 mL, 10 N). The mixture was extracted with EtOAc (3×3 mL). The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. The oil residue was purified by flash column chromatography (10% MeOH in CH_2Cl_2) to afford **6** as a colorless or tan oil. Compound **6a** (67%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.20 (m, 1H), 7.20–7.02 (m, 2H), 7.02–6.82 (m, 4H),

3.76–3.66 (m, 1H), 3.54 (t, J = 7.4 Hz, 2H), 3.46–3.24 (m, 3H), 3.10–2.98 (m, 1H), 2.88 (t, J = 7.4 Hz, 2H), 1.62 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.7, 154.1, 148.6, 146.7, 141.7, 140.1, 130.0, 129.9, 124.6, 121.5, 121.4, 116.9, 116.7, 115.9, 115.6, 115.4, 115.3, 113.4, 113.2, 55.9, 54.5, 50.3, 43.7, 33.9; MS: $[M+H]^+$ = 350. Compound **6b** (59%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.18 (m, 6H), 7.00 (d, J = 7.6 Hz, 1H), 6.96–6.84 (m, 2H), 6.60–4.45 (m, 2H), 3.56 (t, J = 7.4 Hz, 2H), 3.28–3.20 (m, 2H), 3.15 (d, J = 4.0 Hz, 1H), 2.98–2.90 (m, 2H), 2.88 (t, J = 7.4 Hz, 2H), 1.51 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.7, 155.4, 142.0, 138.2, 129.9, 129.8, 128.6, 128.0, 127.3, 124.7, 124.6, 115.9, 115.7, 113.2, 113.0, 54.2, 52.7, 51.3, 50.1, 43.6, 34.2; MS: $[M+H]^+$ = 328. Compound **6c** (61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.12 (m, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.90–6.79 (m, 2H), 3.46 (t, J = 7.4 Hz, 2H), 3.32–3.10 (m, 5H), 3.00–2.84 (m, 2H), 2.80 (t, J = 7.4 Hz, 2H), 1.63 (br, 2H), 1.48–1.38 (m, 2H), 1.30–1.18 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.6, 155.1, 142.1, 142.0, 129.8, 124.6, 115.8, 115.6, 113.1, 112.9, 54.3, 53.2, 50.0, 47.9, 43.6, 34.2, 29.9, 20.0, 13.9; MS: $[M+H]^+$ = 294. Compound **6d** (65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.10 (m, 5H), 3.48 (t, J = 7.4 Hz, 2H), 3.45–3.37 (m, 1H), 3.26–3.16 (m, 4H), 3.10–2.98 (m, 1H), 2.92–2.84 (m, 1H), 2.81 (t, J = 7.4 Hz, 2H), 1.72 (br, 2H), 0.98–0.82 (m, 1H), 0.48–0.33 (m, 2H), 0.22–0.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 139.5, 128.9, 128.4, 126.2, 54.3, 53.2, 52.2, 50.3, 43.6, 34.5, 9.7, 3.3; MS: $[M+H]^+$ = 274. Compound **6e** (52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.11 (m, 5H), 4.32–4.15 (m, 1H), 3.48 (t, J = 7.4 Hz, 2H), 3.30–3.00 (m, 3H), 2.94–2.85 (m, 2H), 2.83 (t, J = 7.4 Hz, 2H), 2.20–1.50 (m, 7H), 1.43–1.16 (m, 4H), 1.10–0.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 139.5, 128.9, 128.4, 126.2, 53.9, 52.9, 50.5, 46.9, 43.6, 34.4, 30.3, 25.8, 25.7; MS: $[M+H]^+$ = 302.

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11. Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.04–7.89 (m, 2H), 7.72–7.66 (m, 1H), 7.46–7.40 (m, 1H), 7.26–7.20 (m, 2H), 7.10–6.84 (m, 4H), 4.19 (t, J = 7.4 Hz, 2H), 3.97 (s, 3H), 2.93 (br, 2H), 2.58 (br, 2H), 1.62–1.52 (m, 2H), 1.36–1.25 (m, 2H), 0.92 (t, J = 7.0 Hz, 3H); MS: $[M+H]^+$ = 483.