DIVERSITY OF REARRANGEMENT OF 3-SUBSTITUTED 5-CARBAMOYL-1-PHENYLURACIL DERIVATIVES

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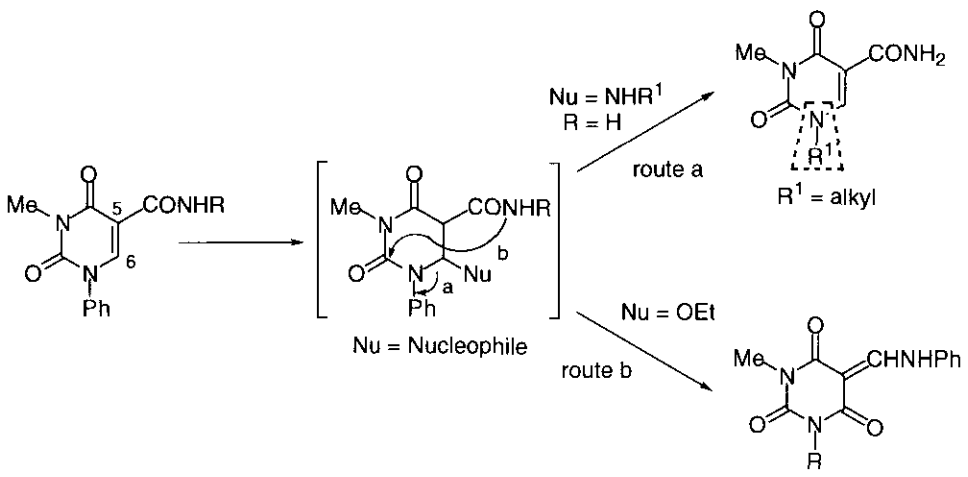
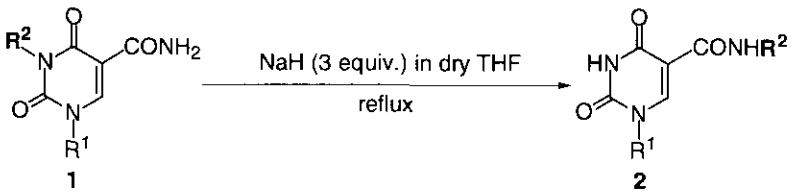
Abstract — Treatment of 3-substituted 5-carbamoyl-1-phenyluracil derivatives (**1a-c**) with NaH afforded 5-(*N*-substituted carbamoyl)-1-phenyluracil derivatives (**2a-c**) *via* rearrangement involving the rare C(2)-N(3) bond cleavage of a uracil ring system. Upon reaction of 5-*N*-methylcarbamoyl-1-phenyluracil derivatives (**4a** and **4b**) and 3-methyl-1-phenyl-5-thiocarbamoyluracil (**6**) with NaH, 5-(anilinomethylene)barbituric acid derivatives (**5a, b** and **7**) formed, respectively, *via* rearrangement involving the N(1)-C(2) bond cleavage.

Ring transformations of heterocyclic compounds have been extensively investigated and efficiently utilized as an excellent tool for the synthesis of other heterocycles.[1] It is well known that uracil derivatives react with nucleophiles, such as amines, hydrazines, guanidines and active methylene compounds, to undergo various types of ring transformation.[2] Our previous studies have demonstrated that the reaction of 5-carbamoyl-3-methyl-1-phenyluracils with primary alkylamines and sodium ethoxide causes two types of ring transformation to afford the rearranged 5-carbamoyluracils[3] and 5-anilinomethylene-1-methylbarbituric acids,[4] respectively, *via* a 6-adduct intermediate as shown in Scheme 1. During our study on the reactivity of 3-substituted 5-carbamoyl-1-phenyluracils (**1**), we encountered a novel type of rearrangement in the reaction of **1** with a base lacking nucleophilicity. Thus, treatment of **1a** with 3 molar equivalents[5] of NaH in dry THF led to the formation of 5-*N*-methylcarbamoyl-1-phenyluracil (**2a**) in 94% yield. The structure of the product (**2a**) was presumed by the spectral data and microanalytical result.



Scheme 1

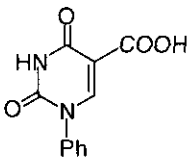
Table 1. Formation of 5-(*N*-substituted carbamoyl)uracil derivatives (**2a-c**).



Compound	R^1	R^2	Time (h)	Product	Yield (%)
1a	Ph	Me	3	**2a**	94
1b	Ph	Et	4.5	**2b**	95
1c	4-BrC_6H_4	Me	3	**2c**	57
1d	Me	Me	24	**2d**	0[a]

[a] The starting material (**1d**) was recovered.

The ultimate proof of the structure was provided by an alternative synthesis of **2a** from 5-carboxy-3-methyl-1-phenyluracil (**3**) and $MeNH_2$. Analogous reactions of 3-ethyl-1-phenyl- and 3-methyl-1-(4-bromophenyl)-5-carbamoyluracil derivatives (**1b** and **1c**) gave the corresponding rearrangement products (**2b** and **2c**) as shown



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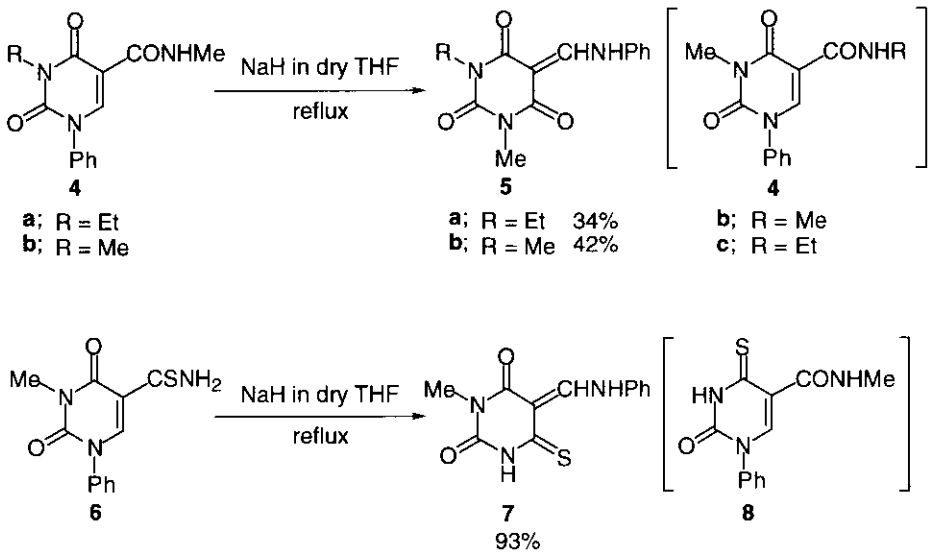
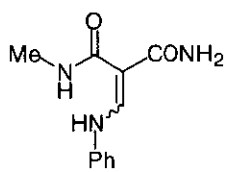
in Table 1. The present reaction seemingly involves a rearrangement of the N(1) substituent on the uracil ring to the nitrogen of the 5-carbamoyl group. On the other hand, treatment of 5-carbamoyl-1,3-dimethyluracil (**1d**) with NaH under reflux conditions resulted in the recovery of the starting material (**1d**).



Scheme 2

The present rearrangement reaction was applied to 3-ethyl-5-*N*-methylcarbamoyl-1-phenyluracil (**4a**), possessing different substituents at the N(3)- and the nitrogen of the 5-carbamoyl group, expecting the formation of 5-*N*-ethylcarbamoyl-3-methyl-1-phenyluracil (**4c**). However, no formation of **4c** was observed and the isolated product was 5-anilinomethylene-1-ethyl-3-methylbarbituric acid (**5a**).[6] This reaction seemed to be the same type of rearrangement of the 5-carbamoyluracil into the barbituric acid as described previously (see Scheme 1),[4] although no nucleophile was used. Therefore, analogous reaction of **4b** was tried to give the corresponding barbituric acid (**5b**),[6] which was identical with the sample prepared by the reaction of **4b** with sodium ethoxide.[4b] Similar treatment of the 5-thiocarbamoyluracil (**6**), which has no substituent at the 5-thiocarbamoyl group, afforded a 4-thiobarbituric acid (**7**)[4b] in 93% yield and no formation of the expected rearrangement product, 5-*N*-methylcarbamoyl-1-phenyl-4-thiouracil (**8**), was observed in the reaction mixture (Scheme 2). Upon treatment of **1a** with NaOH as a base instead of NaH



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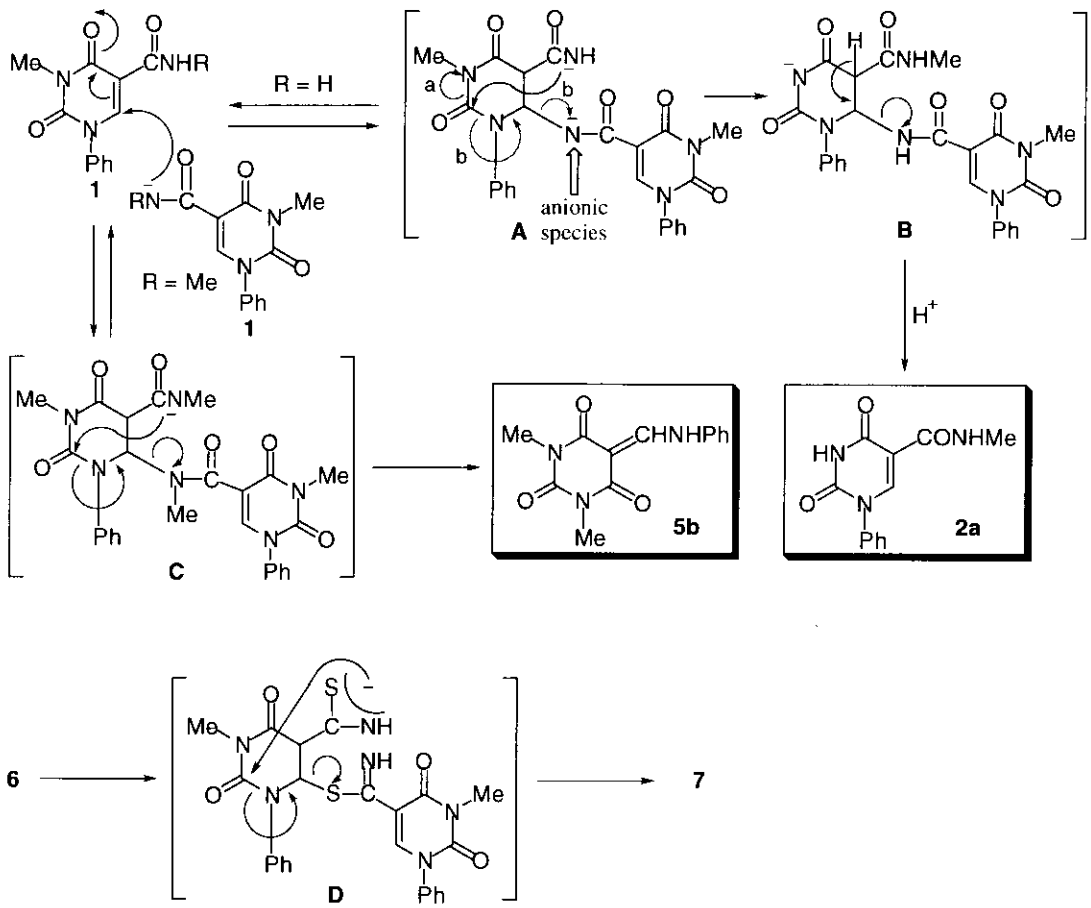
under the same conditions, an open-chain product, acrylamide derivative (**9**) was exclusively obtained in 66% yield. The conversion of **1a** into **9** could involve attack of the hydroxide ion at the C(2) position, followed by the decarboxylation.[3b]



Scheme 3

On the basis of these results, a plausible reaction sequence for the present ring transformations is outlined in Scheme 3. In the both rearrangement, the employed 5-carbamoyluracils (**1**, **4** and **6**) themselves would act a nucleophile in the presence of NaH. When the 5-(*N*-unsubsutituted carbamoyl)uracil (**1a**, R = H) was used as the starting material, an initial nucleophilic attack on the 6-position by the carbamoyl anion of **1a** could give rise to a Michael adduct (**A**). The conversion of the sp^2-carbon into sp^3-carbon at the 5-position facilitates an intramolecular nucleophilic attack of the 5-carbamoyl anion on the 2-carbonyl carbon

followed by cleavage of the C(2)-N(3) bond (pathway a) to give the 5-*N*-methylcarbamoyluracil (**2a**). The ring transformation involves the displacement of the N(3)-C(4) moiety of the uracil by the 5-carbamoyl group. This is ascribed to the formation of an anion on the nitrogen at the C(6) position of **A**. The presence of an anionic species of **A** in the presence of NaH would prevent the N(1)-C(2) bond cleavage (pathway b) induced by attack of the 5-carbamoyl group on the 2-position and allow the C(2)-N(3) bond to be cleaved (pathway a). On the other hand, the Michael adducts (**C** and **D**) that can not form the corresponding anionic species at the C(6) substituent were preferentially cleaved in the N(1)-C(2) bond to give the barbituric acids (**5b** and **7**) as reported previously.[4]

EXPERIMENTAL

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All column chromatography was carried out with silica gel (230–400 mesh, MERCK). All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (MERCK), and compounds were visualized under UV light (254 nm). Melting points were determined on a Yanagimoto micro hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were determined with a JEOL GX-270 or EX-400 spectrometer using sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) in DMSO-d_6 as an internal standard. Coupling constants (J) are reported in Hertz (Hz). UV spectra were obtained from EtOH solutions on a Shimadzu UV-260 spectrophotometer. MS were obtained in a JEOL JMS-D 300 machine operating at 70 eV. Microanalyses were carried out at the Microanalytical Laboratory of our university.

5-Carbamoyl-3-ethyl-1-phenyluracil (1b). To a stirred suspension of 5-carbamoyl-1-phenyluracil[7] (3.29 g, 14.24 mmol) and K_2CO_3 (2.17 g, 15.62 mmol) in DMF (30 mL) was added ethyl iodide (1.25 mL, 15.62 mmol) at rt. The reaction mixture was stirred at rt for 2 h and the solvent was evaporated *in vacuo*. The residue in water (20 mL) was acidified with 10% $NaHSO_4$ solution to pH 3 and the resulting precipitate was filtered to give **1b** (3.65 g, 99%). The analytical sample was recrystallized from MeOH: mp 203.5-205.5 ℃; MS (EI$^+$) m/z 259 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.1 Hz), 4.11 (q, 2H, J = 7.1 Hz), 5.84 (br, 1H), 7.25-7.60 (m, 5H), 8.52 (s, 1H), 8.67 (br, 1H). *Anal.* Calcd for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.07; H, 5.22; N, 16.05.

1-(4-Bromophenyl)-5-carbamoyl-3-methyluracil (1c). A mixture of 1-(4-bromophenyl)-5-cyanouracil[8] (1.00 g, 3.44 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (1.44 mL, 10.31 mmol) in DMF (5 mL) was stirred at rt for 15 h. The solvent was evaporated *in vacuo* and the residue was triturated

with ether. The resulting solid was filtered to give 1-(4-bromophenyl)-5-cyano-3-methyluracil (0.95 g, 86% crude) which was used in the next reaction without further purification.

The crude 1-(4-bromophenyl)-5-cyano-3-methyluracil (0.95 g) in conc. H_2SO_4 (3.4 mL) and water (0.04 mL) was heated at 50 ℃ for 3 h and the reaction mixture was poured over ice. The resulting precipitate was filtered, washed with water and ether and recrystallized from MeOH to give **1c** [0.77 g, 69% for two steps total yield from 1-(4-bromophenyl)-5-cyanouracil]: mp >300 ℃; MS (EI^+) m/z 323 (M^+); ^1H NMR (DMSO-d_6) δ 3.42 (s, 3H), 7.55 (d, 2H, J = 8.8 Hz), 7.77 (br, 1H), 7.83 (d, 2H, J = 8.8 Hz), 8.31 (br, 1H), 8.36 (s, 1H). *Anal.* Calcd for $C_{12}H_{10}N_3O_3Br$: C, 44.47; H, 3.11; N, 12.96. Found: C, 44.44; H, 3.08; N, 12.85.

5-(*N*-Substituted carbamoyl)-1-phenyluracil Derivatives (2a-c). ***General procedure (Table 1).*** A mixture of the 5-carbamoyl-1-phenyluracil derivatives (**1a**[7]-**c**) (1 equiv.) and sodium hydride (60% W/W in mineral oil, 3 equiv.) in dry THF (8.0 mL per 1 mmol of the starting material) was refluxed for the reaction time specified in Table 1. The solvent was evaporated *in vacuo* and the residue in water (2 mL per 1 mmol of the starting material) was acidified with conc. HCl to pH 3. The resulting precipitate was filtered and recrystallized from an appropriate solvent, giving the 5-(*N*-substitued carbamoyl)-1-phenyluracil derivatives (**2a-c**).

5-*N*-Methylcarbamoyl-1-phenyluracil (2a): 94%; mp >300 ℃ (from AcOH-H_2O); MS (EI^+) m/z 245 (M^+); ^1H NMR (DMSO-d_6) δ 2.89 (d, 3H, J = 4.7 Hz), 7.55-7.80 (m, 5H), 8.28 (s, 1H), 8.70 (br d, 1H, J = 4.7 Hz), 12.10 (br, 1H). *Anal.* Calcd for $C_{12}H_{11}O_3N_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.88; H, 4.52; N, 17.00.

5-*N*-Ethylcarbamoyl-1-phenyluracil (2b): 95%; mp 252-256 ℃ (from EtOH); MS (EI^+) m/z 259 (M^+); ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, J = 7.3 Hz), 3.37-3.53 (m, 2H), 7.25-7.58 (m, 5H), 8.53 (s, 1H), 8.57 and 8.85 (each br, 1H). *Anal.* Calcd for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.18; H, 5.06; N, 16.03.

1-(4-Bromophenyl)-5-*N*-methylcarbamoyluracil (2c): 57%; mp >300 ℃ (washed with hot MeOH); MS (EI^+) m/z 323 (M^+); ^1H NMR (DMSO-d_6) δ 2.79 (d, 3H, J = 4.9 Hz), 7.46 and 7.72 (each d, 2H, J = 8.5 Hz), 8.20 (s, 1H), 8.60 (br, 1H), 12.02 (br, 1H). *Anal.* Calcd for $C_{12}H_{10}N_3O_3Br$: C, 44.47; H, 3.11; N, 12.96. Found: C, 44.30; H, 3.12; N, 12.92.

Alternative Synthesis of 5-*N*-Methylcarbamoyl-1-phenyluracil (2a). A mixture of 5-carboxy-1-phenyluracil (**3**)[9] (1.16 g, 5.0 mmol) and $MeNH_2$ (30% in MeOH, 0.52 mL, 6.0 mmol) in dry DMSO and dry DMF (each 5.0 mL) was added DPPA[10] (1.29 mL, 6.0 mmol) at rt, after which it was stirred for 1 h. The reaction mixture was poured into water (50 mL). The resulting precipitate was

filtered and washed with H_2O and EtOH and recrystallized from EtOH to give **2a** (0.34 g, 28%).

3-Ethyl-5-*N*-methylcarbamoyl-1-phenyluracil (4a). A suspension of **1b** (1.00 g, 3.86 mmol) in AcOH (10 mL) and conc. HCl (10 mL) was refluxed for 27 h. The solvents were evaporated *in vacuo* and the residue was triturated with water (10 mL). The resulting precipitate was filtered and washed with water (5mL x 3) to give 5-carboxy-3-ethyl-1-phenyluracil (0.70 g, 70% crude). The product was used for the next reaction without further purification.

To a mixture of the crude 5-carboxy-3-ethyl-1-phenyluracil (0.70 g, 2.69 mmol) and $MeNH_2$ (40% in MeOH, 0.19 mL, 2.69 mmol) in dry DMF (10 ml) was added DPPA[10] (0.58 mL, 2.69 mmol) at rt, after which it was stirred for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between AcOEt (50 mL) and water (25 mL). The organic layer was washed with saturated $NaHCO_3$ solution (25 mL), H_2O (25 mL) and brine (25 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from EtOH to give **4a** (0.38 g, 36% for two steps total yield from **1b**): mp 149-152 ℃; MS (EI^+) m/z 273 (M^+); ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.1 Hz), 2.97 (d, 3H, J = 4.9 Hz), 4.10 (q, 2H, J = 7.1 Hz), 7.10-7.60 (m, 5H), 8.50 (s, 1H), 8.82 (br, 1H). HRMS (EI) calcd for $C_{14}H_{15}N_3O_3$ (M^+) 273.1113, found 273.1107.

5-(Anilinomethylene)barbituric Acid Derivatives (5a, b and 7). *General procedure.* A mixture of the 1-phenyluracil derivatives (**4a, b**[4b] and **6**[4b]) (1 equiv.) and sodium hydride (60% W/W in mineral oil, 3 equiv.) in dry THF (8.0 mL per 1 mmol of the starting material) was refluxed for the reaction time specified below. The reaction mixture was treated as described below unless otherwise stated. The solvent was evaporated *in vacuo* and the residue in water (2 mL per 1 mmol of the starting material) was acidified with conc. HCl to pH 3. The resulting precipitate was filtered and recrystallized from an appropriate solvent, giving the 5-(anilinomethylene)barbituric acid derivatives (**5a, b** and **7**).

5-Anilinomethylene-1-ethyl-3-methylbarbituric Acid (5a). The mixture was refluxed for 3 h and the neutralized solution was extracted with AcOEt. The extracts were evaporated *in vacuo* and the residue was recrystallized from MeOH to give **5a** (34%): mp 134-136.5 ℃; MS (EI^+) m/z 273 (M^+); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 6.8 Hz), 3.37 (s, 3H), 4.03 (q, 2H, J = 6.8 Hz), 7.05-7.34 (m, 3H), 7.34-7.50 (m, 2H), 8.71 (d, 1H, J = 13.7 Hz), 12.12 (br, 1H). *Anal.* Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.48; H, 5.60; N, 15.32.

5-Anilinomethylene-1,3-dimethylbarbituric Acid (5b). The mixture was refluxed for 3 h and the crude precipitate was recrystallized from MeOH to give **5b** (42%). This product was identical with an authentic sample.[4b]

5-Anilinomethylene-1-methyl-4-thiobarbituric Acid (7). The mixture was refluxed for 14.5 h, after which it was concentrated *in vacuo*. The resulting precipitate was filtered to give **7** (93%) and recrystallized from MeOH. This product was identical with an authentic sample.[4b]

2-Carbamoyl-3-phenylamino-*N*-(methyl)acrylamide (9). A mixture of **1a**[7] (200 mg, 0.82 mmol) and sodium hydroxide (97.8 mg, 2.46 mmol) in THF (5.0 mL) was refluxed for 40 min, after which it was concentrated *in vacuo*. The residue in ice-water (2 mL) was acidified with conc. HCl to pH 3. The resulting precipitate was filtered to give **9** (118 mg, 66%): mp 153.5-155.5 ℃; MS (EI$^+$) m/z 219 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 2.90 (d, 3H, J = 4.9 Hz), 5.25 (br, 2H), 6.90-7.40 (m, 5H), 7.89 (d, 1H, J = 12.2 Hz), 9.00 (br, 1H), 12.08 (br d, 1H, J = 12.2 Hz). *Anal.* Calcd for $C_{11}H_{13}N_3O_2$: C, 60.25; H, 5.98; N, 19.17. Found: C, 59.99; H, 5.84; N, 18.97.

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5 The reaction using 1 molar equivalent of NaH did not go to completion. Therefore, we applied 3 equivalents of NaH for the rearrangement taking into account the convenience for a progress of the reaction.

6 For convenient drawings, the rearrangement products are represented as the barbituric acid forms (**5** and **7**). Unchanged starting materials (**5a**) and (**5b**) were not detected in the reaction mixture.

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