# Diversity of the C–C Bond Formation in the Reaction of a 5-Bromouracil Derivative with Carbanions

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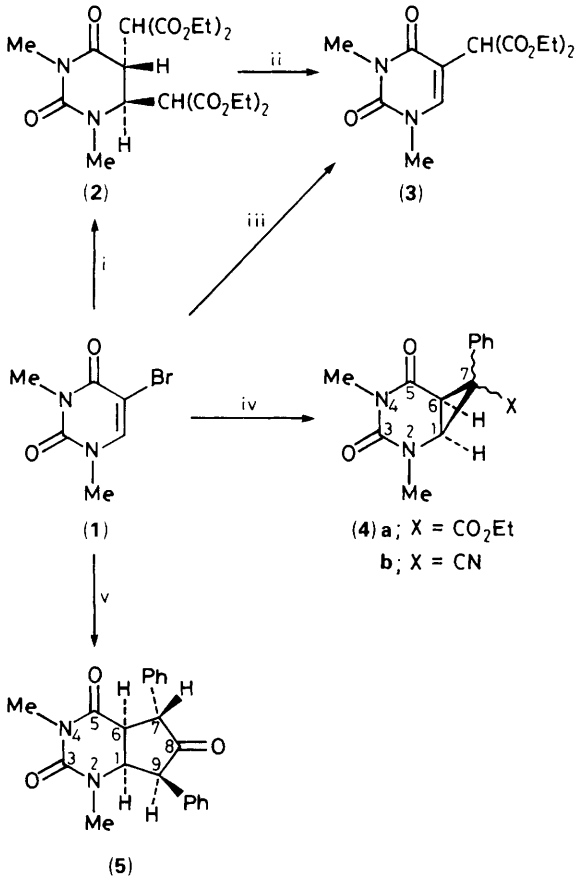
The reaction of 5-bromo-1,3-dimethyluracil (**1**) with active methylene compounds in the presence of base gave 5,6-disubstituted 5,6-dihydrouracil derivative (**2**), 2,4-diazabicyclo[4.1.0]heptane derivatives (**4**), and 2,4-diazabicyclo[4.3.0]nonane derivative (**5**), the formation of which was significantly dependent on the nature of the carbanions.

Synthetic and biological interest has generated much effort towards the introduction of carbon functions at the 5-position of the uracil ring.[1] The employment of coupling between readily available 5-bromouracils and various carbanions is a primary strategy for this purpose. The only successful example, however, has been reported by Ueda *et al.*; the reaction of a 5-bromouridine derivative with a malonate carbanion results in the formation of 5-(malonate-substituted)uridine.[2]



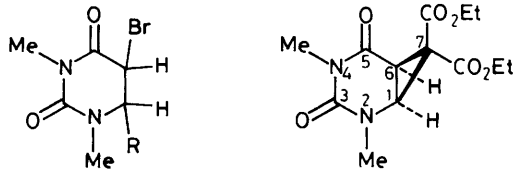

**Scheme 1.** *Synthetic procedure:* active methylene compounds (3 equiv.) allowed to react with (**1**) (1 equiv.) in the presence of NaOEt (3 equiv.) in absolute EtOH. Compounds (**2**)—(**5**) were separated by silica gel column chromatography. *Reagents and conditions:* i, $CH_2(CO_2Et)_2$, NaOEt, room temp., 2 h, (**2**) was recrystallized from ether; ii, NaOEt, room temp., 8 h, (**3**) is an oily compound, which was purified by silica gel column chromatography (chloroform); iii, $CH_2(CO_2Et)_2$, NaOEt, room temp., 8 h, iv, $PhCH_2CO_2Et$ or $PhCH_2CN$, NaOEt, room temp., (**4a**) and (**4b**) were recrystallized from ether and chloroform–ether, respectively; v, $(PhCH_2)_2CO$, NaOEt, room temp., 30 min, (**5**) was recrystallized from chloroform–ether.

This prompted us to examine the reaction of 5-bromo-1,3-dimethyluracil (**1**) with carbanions generated from ethyl malonate, ethyl phenylacetate, benzyl cyanide and dibenzylketone to see if this type of functionalisation at the 5-position is versatile. In this communication, we describe that the feature of the C–C bond formation in these reactions is significantly influenced by the nature of carbanions employed and the formation of a C-5-substituted product is rather a rare case among present examples. The present result also provides a new synthetic approach to a novel type of carbocyclic-fused uracil system (Scheme 1).

When (**1**) was allowed to react with diethyl malonate carbanion for 8 h under the conditions described in the footnote to Scheme 1, 5-(malonate-substituted)uracil (**3**) was obtained in 62% yield.

Monitoring by TLC showed the presence of a detectable intermediate during the reaction. In fact, interruption of the reaction after 2 h allowed isolation of the intermediate (41% yield) together with the starting material (**1**). The structure of the intermediate was assigned to 5,6-bis(malonate-substituted)-5,6-dihydrouracil (**2**)† with a *trans*-configuration rather than a *cis*-configuration on the basis of $^1H$ NMR spectral data,‡ *i.e.* no appreciable coupling between H-5 and H-6 in its $^1H$ NMR spectrum was observed.

Treatment of (**2**) (1 equiv.) with sodium ethoxide (3 equiv.) afforded the 5-substituted uracil (**3**) in 67% yield. This result suggests that (**2**) is an intermediate for the formation of (**3**). The intermediate (**2**) can be formed *via* intermolecular nucleophilic attack of the remaining carbanion on the initially formed C-6-adduct (**A**), as was well documented previously in the reaction of uracils with nucleophiles.[3,4] The presence of another cyclopropane intermediate (**B**) possibly formed *via* base-catalysed intramolecular cyclisation of (**A**) was not observed in the present experiment.




R = $CH(CO_2Et)_2$, $PhCHCO_2Et$, PhCHCN, $PhCHCOCH_2Ph$

† All new compounds described herein give satisfactory spectral and microanalytical results consistent with their structures.

‡ $^1H$ NMR ($CDCl_3$) δ 1.20—1.35 (12H, m, CMe), 2.96 and 3.16 (each 3H, each s, NMe), 3.50 (1H, d, *J* 5.6 Hz, C-5–H), 3.66 (1H, d, *J* 7.3 Hz, C-6–CH), 3.75 (1H, d, *J* 5.6 Hz, C-5–CH), 4.15—4.27 (8H, m, $OCH_2$), 4.27 (1H, d, *J* 7.3 Hz, C-6–H); $^{13}C$ NMR 168.28, 166.80, 166.78, 166.17, 166.12, and 152.40 (each C=O), 62.45, 62.34, 62.27, and 62.20 (each $CH_2$), 55.58, 54.49, 51.99, and 44.65 (each CH), 36.54 and 27.78 (each NMe), 13.91, 13.89, 13.87, and 13.80 (each CMe).

It is well known[3] that 5-bromouracils easily react with various nucleophiles to give debromination, 5- and 6-substitution, and ring transformation products. Among them, the formation of the 5-substituted product has been rationalized in terms of an intermediacy of 5,6-disubstituted 5,6-dihydrouracil [*cf.* (**2**)], isolation of which has been unsuccessful. Thus, to our knowledge, the present result is the first example of isolation of such a type of intermediate, leading to 5-substituted uracils.

Contrary to our expectations, when ethyl phenylacetate and benzyl cyanide were employed as a source of carbanions, 2,4-diazabicyclo[4.1.0]heptane derivatives (**4a**) and (**4b**) were isolated as the sole products in 65% and 94% yields, respectively. The structural proof rests upon the presence of C-6–H and C-1–H proton signals in their $^1$H NMR spectra,§ being characteristic of the 2,4-diazabicyclo[4.1.0]heptane system.[5] The cyclopropane ring of (**4a**) was stable upon treatment with base under drastic conditions (reflux for 1 h in the presence of sodium ethoxide or malonate carbanion).

Under analogous conditions, the reaction of (**1**) with dibenzylketone generating a dicarbanion resulted in the formation of 2,4-diazabicyclo[4.3.0]nonane derivative (**5**) in 61% yield. The $^1$H NMR analysis§ suggests that (**5**) adopts a *trans–cis–cis* configuration.¶

The present reactions are most likely explained in terms of the initial formation of C-6-adduct (**A**) from (**1**) followed by inter- or intra-molecular nucleophilic attack of another carbanion species at the 5-position of (**A**). At present, however, the data rationalising the diversity of the C–C bond formation by virtue of the nature of carbanions are not available.

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## References

1 D. E. Bergstrom, *Nucleosides Nucleotides*, 1982, **1**, 1; T. Ueda, in 'Chemistry of Nucleosides and Nucleotides,' ed. L. B. Townsend, Plenum Press, New York, 1988, vol. 1, pp. 1—112.
2 H. Inoue, N. Saito, and T. Ueda, *Chem. Pharm. Bull.*, 1986, **34**, 4585.
3 T. K. Bradshaw and D. W. Hutchinson, *Chem. Rev.*, 1977, **6**, 43.
4 E. G. Sander, in 'Bioorganic Chemistry,' ed. E. E. van Tamelen, Academic Press, New York, 1978, vol. 2, pp. 273—297; B. C. Pal, *J. Am. Chem. Soc*, 1978, **100**, 5170.
5 H. P. M. Thiellier, G. J. Koomen, and U. K. Pandit, *Tetrahedron*, 1977, **33**, 1493.

§ $^1$H NMR ($CDCl_3$) (**4a**); δ 3.23 (1 H, d, *J* 8.8 Hz, C-6–H), 3.73 (1 H, d, *J* 8.8 Hz, C-1–H). (**4b**); 3.04 (1 H, d, *J* 8.3 Hz, C-6–H), 3.54 (1 H, d, *J* 8.3 Hz, C-1–H). (**5a**); δ 3.95 (1H, dd, *J* 8.5 and 2 Hz, C-6–H), 4.13 (1 H, dd, *J* 8.5 and 8Hz, C-1–H), 4.93 (1 H, d, *J* 2 Hz, C-7–H), 5.06 (1 H, d, *J* 8 Hz, C-9–H).

¶ UV spectroscopic data for compounds (**2**)—(**5**); (**2**) m.p. 85—86 °C; UV $\lambda_{max}$ (EtOH) only end absorption. (**3**) Oil; UV $\lambda_{max}$ (EtOH) 269 nm; found $M^+$, 298.1174. $C_{13}H_{18}N_2O_6$ requires *M*, 298.1165. (**4a**) M.p. 123.5—125 °C; UV $\lambda_{max}$ (EtOH) only end absorption (ε > 3000). (**4b**) M.p. 134—135 °C; UV $\lambda_{max}$ (EtOH) only end absorption (ε > 3000). (**5**) M.p. 220—221 °C; UV $\lambda_{max}$ (EtOH) 266 nm.