Free Radical Carboxymethylation of Uracils with Benzoyl Peroxide in Acetic Acid

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Acetic acid solutions of the uracils and benzoyl peroxide were heated at 80 °C to give 5-carboxymethyluracils. Similar treatment of caffeine and benzothiazole gave 8-methylcaffeine and 2-methylbenzothiazole, respectively.

5-Carboxymethyluracil (**2a**)[1] and related compounds[2] are the minor bases of tRNA. Whilst investigating free-radical alkylation of uracils,[3] we found that treatment of uracils (**1**) with benzoyl peroxide in acetic acid at 80 °C under a nitrogen atmosphere gave 5-carboxymethyluracils (**2**). Although (**2a**) and the nucleosides have been synthesized by several groups of workers,[4] the carboxymethylation of uracils provides a simple and effective method for the preparation of (**2**).

An acetic acid solution of uracil (**1a**) or of 6-methyluracil (**1b**) containing benzoyl peroxide when heated at 80 °C under a nitrogen atmosphere gave (**2a**), m.p. > 300 °C (lit.,[5] 316–318 °C) and 5-carboxymethyl-6-methyluracil (**2b**), m.p. > 300 °C (lit.,[6] 329 °C), respectively. Similarly, the reaction of 1,3-dimethyluracils (**1c**) and (**1d**) gave 5-carboxymethyl-1,3-dimethyluracils such as (**2c**), m.p. 167–169 °C and (**2d**), m.p. 190–192 °C together with a small amount of 5-acetoxymethyl-1,3-dimethyluracils (**3c**), m.p. 101–102 °C (lit.,[7] 99.5–100.5 °C), and (**3d**), m.p. 98–100 °C (lit.,[8] 97.5–98 °C). However, attempted carboxymethylation of 1,3-dimethylthymine (**4**) was not successful, the reaction giving (**3c**). On the other hand, when caffeine (**5**) was employed in the reaction with benzoyl peroxide in acetic acid, 8-methylcaffeine (**6**),† m.p. 190–193 °C (lit.,[9] 209 °C) and 8-acetoxymethylcaffeine (**7**), m.p. 157–159 °C were obtained. The reaction of benzothiazole (**8**) also gave 2-methylbenzothiazole (**9**),‡ but (**4**) was not detected from the reaction of (**1c**) (see Table).

The carboxymethylation of uracils is reasonably explained in terms of carboxymethyl radical formation from acetic acid. Although the literature contains several references to the reactions of carboxymethyl radicals, they have been little explored beyond the formation of γ-lactones from olefins and acetic acid.[10] Carboxymethyl radicals were also reported from the pyrolysis of iodoacetic acid.[11] In view of the carboxymethylation of (**1**) and the known ready decarboxylation of phenylacetic acid by radicals,[12] we assume that (**6**) and (**9**) are formed *via* the intermediates, 8-carboxymethylcaffeine and 2-carboxymethylbenzothiazole, respectively. Although free-radical alkylation of aromatic and heterocyclic compounds with carboxylic acids has been reported,[13] a part of those may proceed in the same way as the methylation of (**5**) and (**8**).

Experimental

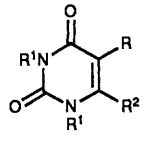
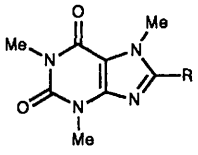
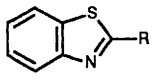
5-Carboxymethyluracils (**2**).—A solution of (**1a**) (112 mg) and benzoyl peroxide [605 mg; obtained from Nakalai tesque (with 25% water) and used without further purification] in acetic acid (50 ml) was heated at 80 °C for 7 h under a nitrogen atmosphere.

† ^{1}H and ^{13}C NMR of (**6**) were almost identical with those reported.[14]
‡ Product (**9**) was identified by direct comparison with the sample obtained commercially.

Table. Reaction of uracils, caffeine, and benzothiazole with benzoyl peroxide in acetic acid.[a]

Substrate	$(PhCO_2)_2$ (mmol)	Products and isolated yields (%)[b]
(**1a**)[c]	2	(**2a**) (38)
(**1b**)[c]	2	(**2b**) (31)
(**1c**)	1	(**1c**) (29), (**2c**) (65), (**3c**) (2)
(**1d**)	1	(**1d**) (42), (**2d**) (48), (**3d**) (4)
(**4**)	1	(**4**) (60), (**3c**) (14)
(**5**)	1	(**5**) (31), (**6**) (35), (**7**) (3)
(**8**)	2	(**8**) (16), (**9**) (48)

[a] Reaction conditions. Substrate (1 mmol), benzoyl peroxide (1 or 2 mmol), acetic acid (50 ml), 7 h, 80 °C, under N_2. [b] Yield based on the substrate used. [c] Yield of the recovered substrate was not determined.

	R	R^1	R^2		R		R
(**1a**)	H	H	H	(**5**)	H	(**8**)	H
(**1b**)	H	H	Me	(**6**)	Me	(**9**)	Me
(**1c**)	H	Me	H	(**7**)	CH_2OAc		
(**1d**)	H	Me	Me				
(**2a**)	CH_2CO_2H	H	H				
(**2b**)	CH_2CO_2H	H	Me				
(**2c**)	CH_2CO_2H	Me	H				
(**2d**)	CH_2CO_2H	Me	Me				
(**3c**)	CH_2OAc	Me	H				
(**3d**)	CH_2OAc	Me	Me				
(**4**)	Me	Me	H				

The reaction mixture was evaporated to give a solid mass which was extracted with a large amount of chloroform. The residue (144 mg) was shown to be a mixture of (**1a**) and (**2a**) (3:5) by ^{1}H NMR spectroscopy. It was dissolved in dilute NaOH (pH 12.7) and the solution was made acid with dilute HCl (pH 1.7); when set aside for *ca.* 12 h it gave (**2a**) (65 mg) as a white solid.

The separation of the reaction mixture from (**1c**) and (**1d**) was performed by liquid chromatography with a low pressure pump (Fuji gel packed column NQ-2: silica gel 24 mm × 360 mm, with ethyl acetate as eluant).

The structures of the products were fully characterized by ^{1}H and ^{13}C NMR, mass, and UV spectral measurements and elemental analyses.

(**2a**): δ_H([$^2H_6$]-DMSO) 12.17 (br, 1 H), 11.09 (s, 1 H), 10.73 (s,

1 H), 7.36 (s, 1 H), and 3.14 (s, 2 H); δ_C([$^2H_6$]-DMSO) 171.97, 164.11, 151.25, 139.79, 106.65, and 31.31; *m/z* 170 (M^+, 2%), 126 (70), and 112 (100).

(**2b**): δ_H([$^2H_6$]-DMSO) 12.22 (br, 1 H), 11.01 (s, 1 H), 10.76 (s, 1 H), 3.21 (s, 2 H), and 2.02 (s, 3 H); δ_C([$^2H_6$]-DMSO) 171.98, 164.06, 150.63, 149.62, 103.63, 29.54, and 16.04; *m/z* 184 (M^+, 1%), 140 (100), and 126 (60).

(**2c**): δ_H($CDCl_3$) 7.24 (s, 1 H), 3.40 (s, 2 H), 3.42 (s, 3 H), and 3.37 (s, 3 H); δ_C($CDCl_3$) 174.33, 164.02, 151.45, 141.97, 106.21, 37.17, 32.95, and 28.26; *m/z* 198 (M^+, 2%), 154 (100), and 96 (46).

(**2d**): δ_H($CDCl_3$) 3.56 (s, 2 H), 3.46 (s, 3 H), 3.36 (s, 3 H), and 2.28 (s, 3 H); δ_C($CDCl_3$) 174.95, 163.14, 151.91, 150.27, 104.95, 32.45, 31.77, 28.59, and 17.09; *m/z* 212 (M^+, 2%), 168 (100), and 110 (50).

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