# Benzoyltetrazole: a Mild Benzoylating Reagent for Nucleosides

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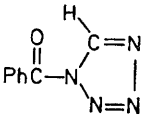
*Summary* Benzoyltetrazole is shown to be an excellent benzoylating reagent for hydroxy-groups in the most common nucleosides; some selectivity between primary and secondary hydroxy-groups and with the primary amino-groups of deoxycytidine and deoxyadenosine or deoxyguanosine was also observed.

BENZOYLATION remains one of the more widely used methods for protecting hydroxy and amino-functions in nucleoside and nucleotide chemistry. However, the most commonly reported reagents, benzoyl chloride–pyridine or benzoic anhydride, often require extended time periods, elevated temperature, or time-consuming work-up procedures. Two alternatives have been reported: benzoyl cyanide, a mild, high-yield reagent reported by Holy *et al.*[1] to be quite general, and benzoylimidazole mentioned by Cramer *et al.*[2] We have demonstrated that (1*H*)-1,2,4-triazole can activate phosphate for nucleophilic attack[3] and more recently have shown that this activation is greatly enhanced by employing (1*H*)-tetrazole.[4] Such derivatives are thus excellent reagents for phosphorylation or condensation in nucleotide chemistry. We now report that the tetrazole system activates the benzoyl group also, thus generating a mild and experimentally simple benzoylating reagent which presumably can be represented by (I).

A typical procedure is as follows: a solution of benzoyl chloride (3—4 mmol) in anhydrous dioxan (15 ml) was added to tetrazole (3—4 mmol) and triethylamine (3—4 mmol) in anhydrous dioxan (5 ml). After 15 min at room temperature, the precipitate ($Et_3NHCl$) was filtered off and



(I)

the filtrate (presumably containing I) added immediately to the appropriate nucleoside (1 mmol) which had been previously rendered anhydrous by repeated evaporations with pyridine. In the case of deoxycytidine or deoxyadenosine, dimethylformamide (2 ml) was added to the solution to increase solubility. A catalytic amount of triethylamine (0·1 mmol) was added and the mixture was shaken at room temperature for a short time then poured into ice–water. Following conventional extraction ($CHCl_3$ or EtOAc) the appropriate product could be crystallised in high yield (90%) from ethanol. In the case of deoxyadenosine and deoxyguanosine, the product crystallised much more rapidly after silica-gel chromatography.

In this manner the following benzoyl derivatives were obtained (nucleoside, time, product and m.p., and isolated yield†): thymidine (dThd), 15 min, Bzo-dThd-oBz, 134—

† All quoted yields are based on amount of starting material taken and are for isolated crystalline products.

135 °C, 94%; deoxycytidine (dCyd), 15 min, Bzo-BzdCyd-oBz,[5] 185—186 °C, 95%; deoxyadenosine (dAdo), 15 min, Bzo-dAdo-oBz, 140—141 °C, 90%; deoxyguanosine (dGuo), 20 min, Bzo-dGuo-OBz (decomposed on heating), 94%; uridine (Urd), 15 min, Bzo-Urd-$(oBz)_2$, 143—144 °C, 96%. All compounds were characterized by n.m.r., u.v., and elemental analysis.

Some interesting selectivities were achieved. With excess of reagent (2 mol. equiv.) the primary amino-group as well as the hydroxy-groups of deoxycytidine was benzoylated while no *N*-benzoylation was detected with deoxyguanosine or deoxyadenosine. When thymidine (1 mmol) was treated with 1·3 mmol of reagent for 40 min the reaction mixture consisted of a mixture of Bzo-dThd-oh (65%) and Bzo-dThd-oBz (17%) indicating that the mildness of the conditions can also permit differentiation between the primary and secondary hydroxy-groups.

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[5] For abbreviations, see *Biochemistry*, 1970, **9**, 4022.