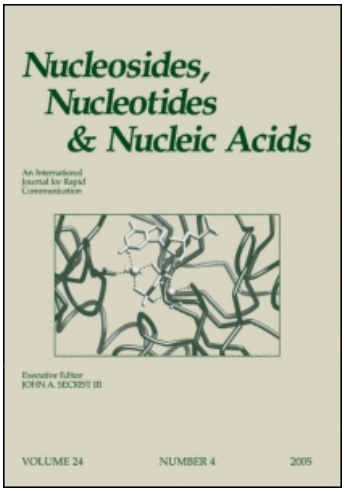

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Ribonucleoside H-Phosphonates. Pyridine *vs* Quinoline - Influence on Condensation Rate

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RIBONUCLEOSIDE H-PHOSPHONATES. PYRIDINE *vs* QUINOLINE - INFLUENCE ON CONDENSATION RATE

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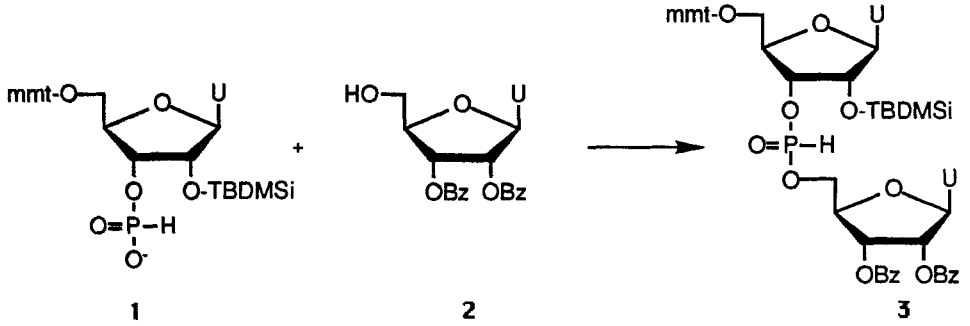

Condensation of 5′-O-monomethoxytrityl-2′-O-t-butyldimethylsilyluridine 3′-H-phosphonate (triethylammonium salt) (**1**) with 2′,3′-O-dibenzoyluridine (**2**) using pivaloyl chloride (PV-Cl)[1], 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide (NPCP)[2] and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (OXP)[2] as condensing agents, has been investigated. Pyridine or quinoline[3] was used as a base and nucleophilic catalyst in the following solvent systems: neat pyridine or quinoline, pyridine (or quinoline)/acetonitrile (4:1, v/v,), pyridine (or quinoline)/acetonitrile (1:1, v/v,), and pyridine (or quinoline)/acetonitrile (1:4, v/v,). Stoicheiometric amounts of **1** and **2** (concentration 25 μM) and 3 equiv. of the appropriate condensing reagent were used in all reactions.

It was found, that using PV-Cl as a coupling agent, the condensations went to completion producing the desired dinucleoside H-phosphonate diester **3** within 1 min (TLC analysis, $CHCl_3$/MeOH 9:1, v/v; R_f(**1**) 0.0, R_f(**2**) 0.32, R_f(**3**) 0.42 and 0.48), irrespective of the solvent composition. At lower concentration of **1** and **2** (12.5 μM), reactions in

quinoline-containing solvents were slightly slower than those carried out in the presence of pyridine (~2 and ~1 min respectively). We noticed also, that reactions in solvents containing 50%, or more, of acetonitrile were slightly faster (ca 10-20%) than those in neat pyridine or quinoline. This was also observed for coupling reactions in which other condensing agents were used.

Reactions in which NPCP was used as an activator proved to be substantially slower than those with PV-Cl. In pyridine-containing solvents, the condensation went to completion within ~15-17 min, however when pyridine was replaced by quinoline, the reaction was not over even when left standing overnight (~16 h).

Also condensation **1** + **2** using OXP was found to be rather slow. In this case, it took ~40-45 min to bring the reaction to completion in pyridine/acetonitrile (1:4, v/v), and ~6 h when quinoline/acetonitrile (1:4, v/v) was used.

It is worth to notice that OXP is significantly more reactive than NPCP as a condensing agent in quinoline-containing solvents, while the opposite reactivity was observed when pyridine, instead of quinoline, was used. No visible catalytic effect of tetrazole or acid catalysts (pyridinium and quinolinium hydrochlorides) on the rate of condensation was observed.

When **1** was replaced by deoxyribonucleoside 3′-H-phosphonates a similar influence of solvents nature on the rate of condensation was observed. Reactions with PV-Cl as a condensing agent had similar rates in pyridine- and in quinoline-containing solvents, but with less reactive coupling agents (OXP, NPCP), condensations were substantially slower in quinoline than in the presence of pyridine.

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3. In quinoline, a predominat formation of deoxyribonucleoside 3′-H-phosphono-acyl anhydride was observed; see V.A. Efimov, I.Y. Dubey, *Bioorg. Khim.*, **16**, 211-218 (1990).