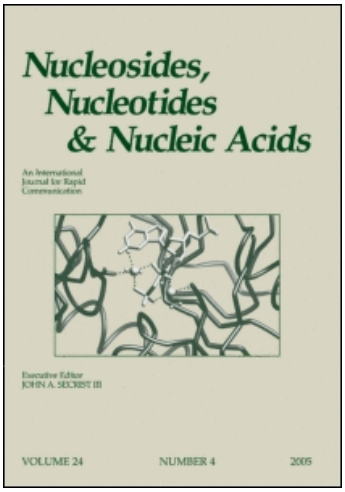


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# Three-phase - Synthesis of Oligonucleotides

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# "THREE-PHASE" - SYNTHESIS OF OLIGONUCLEOTIDES

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SUMMARY: Stable reagents were made from nucleoside-phosphorochloridites and polymeric sec. amines. Treatment of these with tetrazole/$CH_3CN$ and transfer of the resulting solution to immobilized oligonucleotide gave 95% chain elongation.



While phosphoramidite reagents are most valuable for oligonucleotide synthesis, their design is still a compromise between stability and reactivity [1]. For this reason we prepared polymeric reagents from 5'-DMTrdN-$P(OCH_3)Cl$ ( N = common nucleosides ) and polystyrene or silicagel containing $(C_2H_5)NH$- or piperazino groups. When samples of these were treated with tetrazole + acetonitrile, and the solutions syringed [2] to support-bound nucleosides, detritylation yield monitoring and dinucleotide workup indicated near-quantitative internucleotide bond formation. Subsequently, the tetrazole/$CH_3CN$ solution generated from DMTrdT-reagent was fed into an automatic synthesizer and used for the preparation of $dA(T)_4$ and $d(T)_8$ : yields 77% resp. 68% after $C_{18}$-HPLC workup[2] ( ca. 95% per cycle ). In addition to demonstrating the preparative applicability and stability (>1 year) of polymeric phosphoramidites, our studies shed light on the mechanistic role of tetrazole, which may obviously act not only through proton transfer, but also, by nucleophilic attack, generate an active species [3], which is now further investigated.

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