Tetrahedron Letters No. 16, pp 1353 - 1354, 1973. Pergamon Press. Printed in Great Britain.

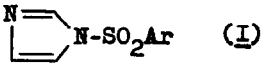
ARENESULFONYL IMIDAZOLIDES, NEW REAGENTS FOR POLYNUCLEOTIDE SYNTHESIS

Yu.A.Berlin, O.G.Chakhmakhcheva, V.A.Efimov, M.N.Kolosov, V.G.Korobko

(Shemyakin Institute for Chemistry of Natural Products,
USSR Academy of Sciences, Moscow, USSR)

(Received in UK 6 February 1973; accepted for publication 8 March 1973)

In non-enzymic polynucleotide synthesis, dicyclohexylcarbodiimide and arenesulfonyl chlorides were heretofore the only reagents successfully used to effect formation of the 3',5'-phosphodiester bond (1). We have found arenesulfonyl imidazolides (I) to be another group of reagents useful for chemical synthesis of oligo- and polynucleotides.



(I)

The imidazolides I are easily prepared in almost quantitative yield from the corresponding chlorides by reaction with one equivalent each of imidazole and triethylamine in chloroform solution or by the procedure of Staab et al. (2). Three of the imidazolides have been found suitable for activating phosphomonoester groups of nucleotides, namely p-toluenesulfonyl imidazolide (TsI; m.p.78-79°, cf. (2)), mesitylenesulfonyl imidazolide (MSI; m.p.97-99°), and 2,4,6-triisopropylbenzenesulfonyl imidazolide (TPSI; m.p.116-117°). They induce condensation of appropriately protected deoxyribonucleotides at 3'-hydroxyl and 5'-phosphate groups, thus differing from carbonyldiimidazole which was reported to be ineffective in formation of the 3',5'-internucleotide linkage (3). As compared with the corresponding chlorides, the imidazolides I induce internucleotide condensation much slower but cause no darkening of the reaction mixture, do not affect acid-sensitive bonds in trityl derivatives, and do not react with 3'-hydroxyls (no sulfonylation products were detected after 3'-unprotected nucleotides were kept in pyridine solution with large excess of TsI, MSI or TPSI for a week at 20°). TsI and MSI are similar in their condensing capacities, while TPSI is appreciably less active.

The use of these reagents for polynucleotide synthesis is illustrated by the Table wherein examples of MSI-induced condensations are presented, MSI having been investigated in this laboratory more than the other imidazolides. The syntheses were carried out with 0.01 to 10 mmoles of reactants. In each case two molar equivalents of MSI were used, the 3'OH- and 5'P-components being taken in approximately stoichiometric amounts as 0.1-0.3 M solution in dry pyridine. The condensation proceeded for 5-6 days at room temperature, the time could be reduced to one half by use of a ten-fold excess of MSI (addition of dry Dowex 50 did not accelerate the reaction). After condensation the reaction mixture was mildly treated with NaOH to remove alkali-sensitive protecting group(s), and the resultant nucleotide was isolated by chromatography on DEAE-cellulose or on silica gel and analyzed (before and after removal of N-protecting groups) by the Tomlinson-Tener procedure (4) and spectrophotometrically and enzymatically.

Table [a]

Starting material		Resultant nucleotide	Yield %
3'OH-Component	5'P-Component		
dCEpT	dpT-Ac	dpTpT	58
dCEpT	dpT-Ac [b]	dpTpT	82
dMMTrG^{Bz}	dpT-Ac	dMMTrG^{Bz}pT	60
dMMTrA^{Bz}	dpC^{An}-Ac	dMMTrA^{Bz}pC^{An}	52
dCEpTpG^{iB}	dpG^{iB}-iB	dpTpG^{iB}pG^{iB}	63
dMMTrG^{Bz}	dpTpT-Ac	dMMTrG^{Bz}pTpT	50
dCEpG^{iB}pG^{iB}	dpTpTpT-Ac	dpG^{iB}pG^{iB}pTpTpT	38
dMMTrG^{Bz}pTpT	dpC^{An}pTpG^{iB}-Ac	dMMTrG^{Bz}pTpTpC^{An}pTpG^{iB}	34
dCEpG^{iB}pG^{iB}pTpTpT	dpC^{An}pG^{iB}-Ac	dpG^{iB}pG^{iB}pTpTpTpC^{An}pG^{iB}	40
dCEpG^{iB}pG^{iB}pTpTpTpC^{An}pG^{iB}	dpTpG^{iB}pG^{iB}-Ac	dpG^{iB}pG^{iB}pTpTpTpC^{An}pG^{iB}pTpG^{iB}pG^{iB}	25

[a] iB stands for isobutyryl; for other abbreviations see (5).

[b] dpT-Ac taken in five-fold excess.

REFERENCES

1. K.L.Agarwal, A.Yamazaki, P.J.Cashion, H.G.Khorana, Angew.Chemie, 84,489 (1972).
2. H.A.Staab, K.Wendel, Chem.Ber., 93, 2902 (1960).
3. T.M.Jacob, H.G.Khorana, J.Am.Chem.Soc., 86, 1630 (1964).
4. G.M.Tener in "Methods in Enzymology. XII. Nucleic Acids. Part A", Academic Press, New York-London, 1967, p.398.
5. A.Kumar, H.G.Khorana, J.Am.Chem.Soc., 91, 2743 (1969).