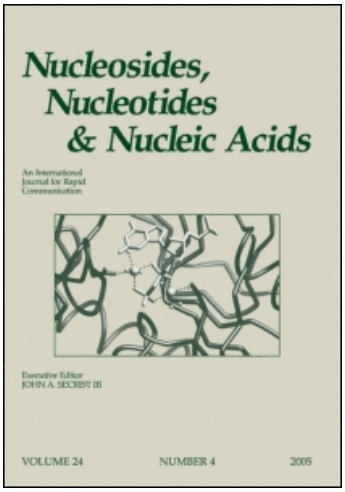

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Arenesulfonylethoxycarbonyl- a Set of Amino Protecting Groups for DNA and RNA Synthesis

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ARENESULFONYLETHOXYCARBONYL- A SET OF AMINO PROTECTING GROUPS FOR DNA AND RNA SYNTHESIS

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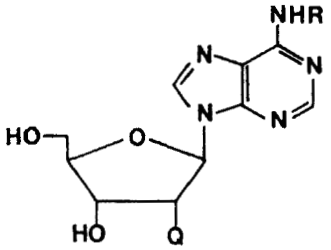
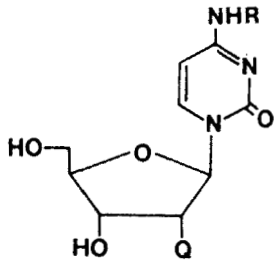
Abstract: *Phenyl-, 4-chlorophenyl- and 4-nitrophenylsufonylethoxycarbonyl groups have been reported for the first time as the exocyclic amino protecting groups in nucleoside chemistry. They are all stable under the standard conditions of manipulations in phosphotriester and phosphiteamidite chemistry, they are removable both under the alkaline hydrolytic conditions and also under the influence of non-nucleophilic tertiary bases. N^3-Phenyl- and 4-toluenesulfonylethoxycarbonyl derivatives of uridine have been also prepared and characterized by ^{15}N-NMR spectroscopy, their stabilities under different conditions have been tested.*

The amino groups of cytosine, adenine and guanine are generally protected in DNA and RNA synthesis with acyl groups which are stable and require extended periods for their removal[1]. Amongst several other exocyclic amino protecting groups which have been proposed for nucleic acid synthesis, N, N-(cyclic & acyclic)amidines[2], aryloxy[3] and alkoxy[3] acetyl groups require relatively shorter deprotection periods. Removal of all of these protecting groups however requires strong alkaline hydrolytic conditions (*i.e.* aqueous ammonia) except for levulinyl[4], benzyloxycarbonyl[5] and 4-nitrophenylsulfenyl[6] groups which are removable respectively with hydrazine hydrate in pyridine-acetic acid (4:1)[4], hydrogenolytically[5] and by thiolate ions[6]. Recently, the syntheses of oligonucleotides containing specific nonionic O-ethyl or O-isopropyl phosphotriester backbones have been shown to be useful as probes[7] to study (a) xenobiotic-induced aberrent replication, transcription, and regulation, (b) nucleic acid-aminoacid interactions involved in recognition process, (c) nuclease resistant inhibitors of translation etc. In view of the recent data that the neutralization of the negative charges of the phosphate groups in a hexathymidylic acid as methylphosphotriesters[8] shows an increased stability of the duplex in aqueous solution and has a close resemblance to the right handed B-DNA, therefore it is likely that the oligonucleotides with nonionic methylphosphotriesters may resemble natural oligo DNA or RNA molecules more closely as probes for above studies. However, a regioselective, high-yielding synthesis of such oligonucleotides with specific nonionic methylphosphotriesters would certainly require exoclic amino protecting groups which are removable under mild and non-alkaline hydrolytic conditions. The need for such specific amino protecting groups has been elegantly demonstrated recently through the synthesis of 3´-aminoacylated-A-C-C[9] fragment of a tRNA molecule and in the preparation of analogues of oligo DNA containing alkali-sensitive N^4,N^4-ethanocytosine[10] residue, using 9-fluorenylmethoxycarbonyl- (Fmoc)[11] group which is



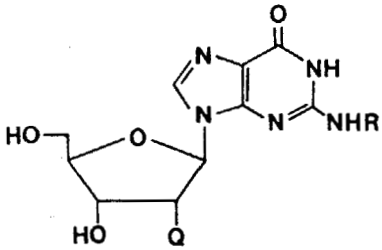
1: R = PSEC; Q = OH
2: R = CPSEC; Q = OH
3: R = NPSEC; Q = OH

9: R = PSEC; Q = H
10: R = CPSEC; Q = H
11: R = NPSEC; Q = H



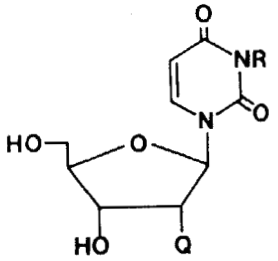
4: R = PSEC; Q = OH
5: R = CPSEC; Q = OH
6: R = NPSEC; Q = OH

12: R = PSEC; Q = H
13: R = CPSEC; Q = H
14: R = NPSEC; Q = H

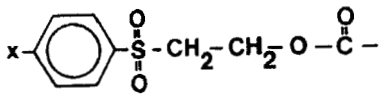


7: R = PSEC; Q = OH
8: R = CPSEC; Q = OH

15: R = PSEC; Q = H
16: R = CPSEC; Q = H



17: R = PSEC; Q = OH
18: R = MPSEC; Q = OH



x = H (PSEC)
x = Cl (CPSEC)
x = NO_2 (NPSEC)
x = Me (MPSEC)

removable by a non-nucleophilic tertiary base. It may be noted that only this β–eliminating group (Fmoc) seems to have fulfilled the stringent requirements in the synthesis of above target molecules more satisfactorily than the 4-nitrophenylethoxycarbonyl[12] group. These have prompted us to examine the properties of different N-substituted arenesulfonylethoxycarbonyl derivatives of adenosine, cytosine, guanosine and their 2′-deoxysugar derivatives. Arene and alkanesufonylethoxycarbonyl groups have however been previously examined for α–amino

group protection in amino acid chemistry[13]. To the best of our knowledge, this paper constitutes the first report of the use of arenesulfonylethoxycarbonyl for exocyclic amino group protection in nucleoside and nucleotide chemistry.

Reaction of arene [phenyl, 4-chlorophenyl & 4-nitrophenyl]sulfonylethylchloroformate with tri-O-(trimethylsilyl) derivatives[14] of adenosine, cytidine, guanosine and the corresponding 2′-deoxy nucleosides, followed by acidic hydrolysis of the TMS groups, gave pure N^6-, N^4- and N^2-protected derivatives in high yields (table 1). A general procedure for the preparation of compounds **1** - **18** is as follows:

Nucleoside (5 mmol) was stringently dried by coevaporations with dry pyridine several times and then dissolved in the same solvent (10 ml / mmol). Trimethylsilyl chloride was added (3 mol equiv./ -OH function in the nucleoside) and stirred for 2 h at RT when a TLC examination [12.5% methanol in CH_2Cl_2] revealed the formation of tri-O-TMS derivatives. To this solution, appropriate arenesulfonylethylchloroformate (1.2 equiv.)* was added and stirred overnight. The reaction was quenched with 5% aq. NH_4HCO_3 and extracted with CH_2Cl_2. Organic layers were pooled and evaporated free of pyridine (coevaporations with toluene). The oily residue was then dissolved in 10% methanolic CH_2Cl_2 [8 ml / mmol] containing 2% benzenesulfonic acid [~0.4 equiv./-OTMS]** and stirred for ~2 min at RT. Volatile matters were evaporated and the residue was dissolved in a small volume of methanol, diluted with CH_2Cl_2, and loaded onto a short silica gel column made up with CH_2Cl_2. The column was eluted in step gradients (0 - 5% methanol). Appropriate fractions were collected to give the desired N-proteced nucleoside in 60 - 95% yield.[* in case of adenine nucleosides, excess of the reagent was added to drive the reaction to completion giving a mixture of mono- & bis-adduct which were separated by chromatography, the bis-adduct subsequently gave the mono-adduct, by controlled (monitored by TLC) alkaline hydrolysis in dioxane-aq. ammonia mixture, which was purified by chromatography. ** [i] in the synthesis of 2′-deoxyadenosine derivatives, the acid (0.05 equiv./-OTMS) solution was added, it was neutralized with Et_3N in CH_2Cl_2 solution at the end of deprotection to avoid depurination. [ii] in case of guanosine and its 2′-deoxy derivatives, 80% aq. acetic acid was used for the hydrolysis of the TMS groups. The hydrolysis was complete in ~90 min.].

Spectroscopic properties of all derivatives are also shown in table 1 while the relative rates of their deprotections both under alkaline hydrolytic and the non-nucleophilic tertiary base promoted conditions [β–elimination] are shown in table 2. Stabilities of all arenesulfonylethoxycarbonyl nucleosides in presence of 80% aqueous acetic acid are shown in table 2, it is clear that the relative rates of depurination of N^6-arenesulfonylethoxycarbonyl-2′-deoxyadenosines are comparable to those found for the corresponding Fmoc derivatives[11].

*Characterization of N^3-arenesulfonylethoxycarbonyl uridines **17** & **18** by ^{15}N-NMR spectroscopy.*

Claesen *et al* [15]reported that the reaction of 4-nitrophenylsulfonylethene with uridine under base catalysed condition gave O^4-[4-nitrophenylsulfonyl]uridine. We have unambiguously shown[16] that the product formed in the latter reaction is not the suggested O^4-substituted product, it is found to be N^3-[4-nitrophenylsulfonylethyl]uridine by ^{15}N-NMR spectroscopy; ^{13}C-NMR data have also supported this structural assignment[17,18]. We have observed in our ^{15}N-NMR studies[16] that the N^3 chemical shift profoundly changes as a result of O^4 versus N^3 substitution since its state of hybridization changes from sp^3 to sp^2 in N^3- & O^4-substituted products, respectively. Thus the N^3 in N^3-benzoyluridines and N^3-alkyluridines absorb at ~-193 and ~-222 ppm, respectively, while it absorbs at ~-153 ppm in O^4-substituteted uridines. The N^3 of arenesulfonylethoxycarbonyluridines **17** & **18** absorb at -197.4 & -197.4 ppm respectively while the N^1 in corresponding compounds absorb at -236.9 & -237.0 ppm. Clearly the effect of the electron-withdrawing acyl group is reflected on the chemical shifts of the N^3 in compounds **17** & **18**, as in N^3-benzoyluridine, suggesting the unambiguities of their structures.

Table 1: Yields & spectroscopic properties of compounds 1 - 18.

Compounds	yield (%) [mp °C]	UV (nm)	^{1}H-NMR [δ]	^{13}C-NMR *(sugar-carbons are not included)* [δ]
1.	85 [136-7]	266 (sh), 272 [pH 2], 260 (sh), 267 [pH 7], 258, 263, 270 (sh), 292, 298 [pH 12]	8.62 (s, 1H), 8.25 (s, 1H), 8.1-7.6 (m, 5H), 5.97 d, 7.2 Hz, 1H), 5.0-4.8 (m, 1H), 4.61 (t, 5.9 Hz, 2H), 4.5-4.3 (m, 2H), 4.1-3.8 (m, 2H), 3.59 (t, 5.9 Hz, 2H)	152.7 (C2), 149.4 (C4), 123.8 (C5), 151.7 (C6), 142.9 (C8), 151.7 (C=O)
2.	62 [118-9]	224, 272 (sh), 276 [pH 2], 230 (sh), 269, 276 (sh) [pH 7], 229 (sh), 260, 275 (sh), 292, 298 [pH 12]	8.65 (s, 1H); 8.26 (s, 1H), 8.0-7.4 (m, 4H), 5.94 (d, 6.3 Hz, 1H), 4.9-4.5 (m, 4H), 4.4-4.1 (m, 2H) 4.1-3.2 (m, 3H)	151.7 (C2), 149.5 (C4), 123.8 (C5), 151.7 (C6), 143.1 (C8), 151.7 (C=O)
3.	60 [124-5]	257, 268 (sh) [pH 2], 257, 266 (sh) [pH 7], 257, 304 (sh) [pH 12]	8.62 (s,1H), 8.4-8.1 (m, 4H), 8.25 (s, 1H), 5.98 (d, 5.4 Hz, 1H), 5.7-5.5 (m, 1H), 5.1-4.7 (m, 2H), 4.65 (t, 5.4 Hz, 2H), 4.6-3.6 (m, 5H), 3.75 (t, 2H)	151.5 (C2), 149.2 (C4), 123.7 (C5), 151.5 (C6), 142.9 (C8), 151.8 (C=O)
4.	95 [136-7]	238, 265, 272, 305 [pH 2], 242, 265 (sh), 273, 295 [pH 7], 266 (sh), 272, 277 (sh) [pH 12]	8.43 (d, 8.1 Hz, 1H), 8.0-7.5 (m, 5H), 7.05 (d, 8.1 Hz, 1H), 5.85 (d, 1.0 Hz, 1H), 5.3 (m, 1H), 4.7 (m, 1H), 4.49 (t, 6.3 Hz, 2H), 4.3-4.2 (m, 3H), 3.8-3.4 (m, 2H), 3.56 (t, 6.3 Hz, 2H)	154.6 (C2), 162.6 (C4), 94.5 (C5), 145.1 (C6), 152.8 (C=O)
5.	95 [165-6]	230, 262 (sh), 270 (sh), 276 (sh), 305 [pH 2], 231, 270 (sh), 277 (sh), 294 [pH 7] 250 (sh), 257 (sh), 264 (sh), 269, 274 [pH 12]	8.7 (d, 7.2 Hz, 1H), 8.0-7.4 (m, 4H), 7.1 (d, 7.2 Hz, 1H), 5.89 (s, 1H), 4.53 (t, 6.3 Hz, 2H) 4.5-3.3 (m, 10H)	154.5 (C2), 162.5 (C4), 94.4 (C5), 145.1 (C6), 152.7 (C=O)
6.	64 [146-7]	242, 299 [pH 2], 242, 291 [pH 7], 250 [pH 12]	8.42 (d, 7.2 Hz, 1H), 8.5-8.1 (m, 4H), 6.85 (d, 7.2 Hz, 1H), 5.76 (s, 1H), 5.6-5.5 (m, 1H), 5.3-5.0 (m, 2H), 4.45 (t, 5.4 Hz, 2H), 4.1-2.6 (m, 7H)	154.2 (C2), 162.4 (C4), 94.2 (C5), 145.1 (C6), 152.5 (C=O)
7.	72 [121-2]	255 (sh), 260, 268 (sh), 273, 281 [pH 2], 259, 264, 270 (sh), [pH 7],259 (sh), 264, 270 (sh) [pH 12]	8.15 (s, 1H), 8.0-7.5 (m, 5H), 5.91 (d, 5.4 Hz, 1H), 5.5-4.7 (m, 3H), 4.59 (t, 6.3 Hz, 2H), 4.7-3.5 (m, 5H), 3.65 (t, 6.3 Hz, 2H)	154.1 (C2), 149.4 (C4), 120.4 (C5), 155.5 (C6), 138.4 (C8), 147.4 (C=O)
8.	64 [155-6]	230, 260, 274 (sh) [pH 2], 231, 253 (sh), 258, 275 (sh) [pH 7], 258 (sh), 265 [pH 12]	8.25 (s, 1H), 8.1-7.6 (m, 4H), 5.85 (d, 5.4 Hz, 1H), 4.7-4.3 (m, 3H), 4.3-4.1 (m, 1H), 4.1-3.4 (m, 6H)	154.0 (C2), 149.3 (C4), 120.1 (C5), 155.5 (C6), 138.0 (C8), 147.3 (C=O)
9.	79	267 (sh), 272 [pH 2], 260 (sh), 268 [pH 7], 258, 264, 270 (sh), 293, 298 [pH 12]	8.66 (s, 1H), 8.30 (s, 1H), 8.0-7.5 (m, 5H), 6.48 (dd, 8.6 & 6.3 Hz, 1H), 5.6-5.4 (m, 1H), 5.0-4.8 (m, 1H), 4.7-4.5 (m, 1H), 4.59 (t, 6.3 Hz, 2H), 4.3-4.1 (m, 1H), 4.1-3.7 (m, 2H), 3.62 (t, 6.3 Hz, 2H), 3.0-2.3 (m, 2H)	149.4 (C4), 123.7 (C5), 142.9 (C8), 151.6 (C2, C6 & C=O)

10.	82 [154-5]	272, 275 [pH 2], 268, 276 [pH 7], 258, 261, 292, 298 [pH 12]	8.70 (s, 1H), 8.44 (s, 1H), 8.0-7.4 (m, 4H), 6.49 (dd, 8.1 & 6.3 Hz, 1H), 4.8-4.5 (m, 1H), 4.62 (t, 6.3 Hz, 2H), 4.3-4.1 (m, 1H), 4.0-3.8 (m, 2H), 3.64 (t, 6.3 Hz, 2H), 3.2-2.2 (m, 2H)	151.5 (C2), 149.3 (C4), 123.7 (C5), 151.5 (C6), 142.8 (C8), 151.5 (C=O)
11.	72 [113-4]	262, 268 [pH 2], 255, 264 (sh) [pH 7], 266, 310 (sh) [pH 12]	8.63 (s, 1H), 8.4-8.1 (m, 4H), 8.25 (s, 1H), 6.47 (dd, 8.1 & 5.4 Hz, 1H), 5.5-5.3 (m, 1H), 4.9-4.5 (m, 2H), 4.66 (t, 6.3 Hz, 2H), 4.3-4.1 (m, 1H), 4.1-3.8 (m, 2H), 3.74 (t, 6.3 Hz, 2H), 2.8-2.3 (m, 2H)	151.4 (C2), 149.0 (C4), 123.5 (C5), 151.4 (C6), 142.7 (C8), 151.4 (C=O)
12.	77	235 (sh), 265, 273, 307 [pH 2], 240, 264, 272, 294 [pH 7], 251 (sh), 258 (sh), 266 (sh), 272, 304 (sh) [pH 12]	8.43 (d, 7.2 Hz, 1H), 8.0-7.5 (m, 5H), 7.04 (d, 7.2 Hz, 1H], 6.22 (t, 5.9 Hz, 1H), 4.9-4.1 (m, 3H),4.49 (t, 6.3 Hz, 2H), 4.1-3.6 (m, 3H), 3.57 (t, 6.3 Hz, 2H), 2.7-2.0 (m, 2H)	154.2 (C2), 162.5 (C4), 94.4 (C5), 144.6 (C6), 152.7 (C=O)
13.	95	230, 276 (sh), 306 [pH 2], 230, 276 (sh), 294 [pH 7], 257 (sh), 264 (sh), 269, 272, 306 (sh) [pH 12]	8.42 (d, 7.2 Hz, 1H), 8.0-7.4 (m, 4H), 7.0 (d, 7.2 Hz,1H), 6.21 (t, 6.3 Hz, 1H), 4.9-4.3 (m, 2H),4.49 (t, 6.3 Hz, 2H), 4.1-3.7 (m, 3H), 3.58 (t, 6.3 Hz, 2H), 3.37 (s, 2H), 2.7-2.0 (m, 2H)	154.3 (C2), 162.4 (C4), 94.4 (C5), 144.6 (C6), 152.6 (C=O)
14.	89 [136-7]	250, 304 [pH 2], 243, 295 [pH 7], 251 [pH 12]	8.5-8.1 (m, 5H), 6.94 (d, 7.2 Hz, 1H), 6.17 (t, 6.3 Hz, 1H), 5.2-4.8 (m, 2H), 4.5 (t, 6.3 Hz, 2H), 4.5-3.6 (m, 4H), 3.75 (t, 6.3 Hz, 2H), 2.7-2.0 (m, 2H)	154.0 (C2), 162.3 (C4), 94.1 (C5), 144.7 (C6), 152.5 (C=O)
15.	63 [156-7]	259, 265, 272 [pH 2], 254 (sh), 258, 265 (sh), 272, 280 (sh) [pH 7], 259 (sh), 267, 270 [pH 12]	8.11 (s, 1H), 8.0-7.5 (m, 5H), 6.31 (t, 6.7 Hz, 1H), 4.7-4.4 (m, 4H), 4.1-3.9 (m, 1H), 3.8-3.5 (m, 5H), 2.7-2.1 (m, 2H)	153.9 (C2), 148.7 (C4), 120.1 (C5), 155.2 (C6), 137.9 (C8), 147.0 (C=O)
16.	75 [162-3]	262, 276 (sh) [pH 2], 253 (sh), 257, 276 (sh) [pH 7], 266 [pH 12]	8.16 (s, 1H), 8.0-7.5 (m, 4H), 6.28 (t, 7.0 Hz, 1H), 5.3-4.7 (m, 2H), 4.6-4.4 (m, 3H), 4.1-3.4 (m, 5H), 2.7-2.1 (m, 2H)	153.7 (C2), 148.6 (C4), 119.9 (C5), 155.1 (C6), 137.6 (C8), 146.9 (C=O)
17.	30	265, 259 (sh), 272 (sh) [pH 2], 265, 259 (sh), 272 (sh) [pH 7], 264, 259 (sh), 271 (sh) [pH 12]	8.12 (d, 7.2 Hz, 1H), 8.0-7.5 (m, 5H), 5.88 (d, 4.5 Hz, 1H), 5.69 (d, 7.2 Hz, 1H), 5.2-5.1 (m, 1H), 5.0-4.8 (m, 1H), 4.8-4.6 (m, 1H), 4.67 (t, 6.3 Hz, 2H), 4.2-4.0 (m, 3H), 3.8-3.5 (m, 2H), 3.62 (d, 6.3 Hz, 2H)	148.2 (C2), 157.8 (C4), 101.1 (C5), 141.6 (C6) 149.6 (C=O)
18.	40	258 (sh), 261 (sh), 264, 267, 270 (sh) [pH 2], 262 /sh), 264, 268, 273 (sh) [pH 7], 254 (sh) 257 (sh), 261, 263, 267, 270 (sh) [pH 12]	8.14 (d, 8.1 Hz, 1H), 7.9-7.3 (m, 4H), 5.9 (d, 4.5 Hz, 1H), 5.7 (d, 8.1 Hz, 1H), 4.64 (t, 6.3 Hz, 2H), 4.22-3.9 (m, 3H), 3.9-3.5 (m,4H), 2.43 (s, 3H)	148.1 (C2), 159.7 (C4), 101.0 (C5), 141.5 (C6), 149.5 (C=O)

Table 2: Deprotection of arenesulfonylethoxycarbonyl groups from compounds 1-18.

Compounds	NH_3-morpholine[1]		Et_3N-morpholine[2]		DBU-morpholine[3]		TMG-morpholine[4]		80% aq. CH_3CO_2H
	$t_{1/2}$ [min]	$t_{99.5}$	$t_{1/2}$ [min]	$t_{99.5}$	$t_{1/2}$ [min]	$t_{99.5}$	$t_{1/2}$ [min]	$t_{99.5}$	$t_{1/2}$ [min]
1.*	~10	60	~3300	-	<1	~10	3	22	-
2.*	2	25	1260	-	-	<1	<1	~5	-
3.*	-	3	180	-	-	<1	<1	~3	-
4.*	5	35	480	-	-	<1	<1	10	-
5.*	~1.5	8	360	-	-	<1	-	<1	-
6.*	-	2	65	260	-	<1	-	<1	-
7.*	~40	300	[a]	-	8	60	30	135	-
8.*	~25	150	[a]	-	~2	20	9	80	-
9.	~16	85	5520	-	<1	~7	~4	20	155
10.	~4	30	1620	-	-	~1	<1	5	145
11.	-	3	270	-	-	~1	-	1	150
12.	~5	30	1620	-	-	~2	<1	4	-
13.	~1	10	1140	-	-	~1	-	1	-
14.	-	3	60	-	-	~1	-	1	-
15.	55	330	[a]	-	8	65	30	240	420
16.	~30	-	[a]	-	~1	18	9	80	420
17.	<1	~2	~1	6	-	<1	-	<1	-
18.	<1	~4	~1	9	-	<1	-	<1	-

(1) Aqueous ammonia [d 0.9] in pyridine [1:1, v/v] + morpholine [5 eq.] [20 ml / mmol];
(2) Et_3N [20 eq.] + morpholine [5 eq.] in dry pyridine [20 ml / mmol];
(3) Diazabicycloundecene (DBU) [10 eq.] + morpholine [5 eq.] in dry pyridine [20 ml / mmol];
(4) 1,1,3,3-tetramethylguanidine (TMG) [10 eq.] + morpholine [5 eq.] in dry pyridine [20 ml / mmol];
* stable over 6 h at room temp. in presence of F^- ions in THF-pyridine-water [8:1:1]
[a]: $t_{1/2}$ could not be determined under this condition because the compound precipitated out.

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References:

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and + from Medical University , Pecs, Hungary

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