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NOVEL REGIOSELECTIVE N-ALKYLATIONS OF 5-SUBSTITUTED-2H-TETRAZOLES

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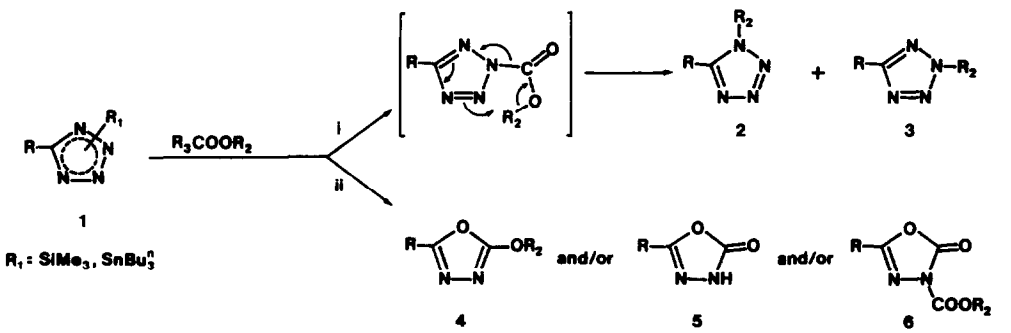
Abstract. Regioselective alkylation of 5-substituted-2H-tetrazoles 1 to 2-alkyl derivatives 3 was achieved *via* decarboxylative alkylation with alkyl cyanoformates. Lesser selectivity was observed with chloroformates.

The search for regioselective alkylation methods for 1,2,4- and 1,2,3-triazoles and 5-substituted tetrazoles is of theoretical and practical interest for the biological activity of the individual isomers[1,2,3,4]. The distribution of alkylation products can be attributed to various kinetically controlled mechanisms. All systems display a common feature, namely, two adjacent nitrogen atoms which may show an α-effect. Most recently, Bentley *et al.* proposed a thermodynamically controlled mechanism of N-alkylation and N-acylation of 1,2,4-triazole, especially favourable for acylation[2].

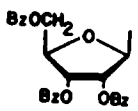
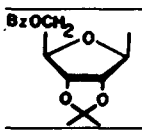


path	R	R_2	R_3
i	protected β-D-ribofuranosyl	Me, Et, allyl, CH_2Ph	CN, Cl
	$(CH_2)_4OAc$	CH_2Ph	Cl
	Ph	Et, CH_2Ph	CN
	$CH_2OCH_2CH_2OBz$	Et	CN
ii	protected β-D-ribofuranosyl	sec-Bu, (-)-menthyl, CH_2CCl_3, CMe_2CCl_3, Ph	Cl
	Ph	Me	Cl
	$CH_2OCH_2CH_2OBz$	Me	Cl
	$(CH_2)_4OAc$	CH_2Ph	Cl

We have been involved in the synthesis of suitably N2 protected 5-substituted tetrazoles which can generate nitrilimines *"in situ"* and are potentially useful synthons for the synthesis of C-nucleosides[3]. The reaction of trimethylsilyl-5-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)tetrazole 1 with ethyl cyanoformate provided 3 (R_2=Et) as a major product instead of the expected cycloadduct. The observed alkylation has been confirmed by using ethyl chloroformate to give a mixture of tetrazoles 2 and 3 (R_2=Et). These findings prompted further investigations so as to make this procedure more general by establishing proper reaction conditions for a regioselective alkylation.

Alkyl chloroformates are generally used as alkoxycarbonylation agents for a variety of compounds[5,6]. Besides, they become N-alkylation agents when reactions are performed on lithium imides[7]. This regioselective principle was later observed on different heterocycles possessing thiol-thione tautomerism[8,9], and on palladium catalyzed allylation *via* allyl enol carbonates[10]. Chloroformates and cyanoformates act as alkylation agents when reacting with 5-β-D-ribofuranosyl and 5-alkyl tetrazoles (pathway *i*), while a competitive rearrangement *via* induced cycloaddition provided 1,3,4-oxadiazoles 4, 5 and 6, with corresponding aryl and alkoxyalkyl tetrazoles and chloroformates (pathway *ii*). The reaction with cyanoformates proceeded exclusively by pathway *i* in a favourable N2/N1 ratio up to 38:1.

Table: Reaction conditions, overall yields and ratios of isomeric N-alkylated tetrazoles.

R	R_2	R_3	Mol.ratio formate/ tetrazole	Temp.	Solv.	Time [hr]	Over. yield [%]	N2/N1 ratio
	Et	CN	20	75°C	A	18	66	5
	CH_2Ph	CN	1.5	refl.	E	2	80	1.2
	Et	Cl	15	refl.	B	30	79	2.2
	Me	Cl	4	r.t.	B	10d	58	2.9
	CH_2Ph	Cl	1.1	refl.	C	18	77	2.6
	allyl	Cl	1.8	refl.	C	23	80	7.6
	Et	CN	15	100°C	A	6	51	25
	Me	Cl	30	refl.	B	36	80	2.2
Ph	Et	CN	2	refl.	D	19	77	38
	CH_2Ph	CN	1.2	refl.	D	5.5	80	7
$BzO(CH_2)_2OCH_2$	Et	CN	3	refl.	D	18	64	2
$AcO(CH_2)_4$	CH_2Ph	Cl	1.1	refl.	C	11	34	1.3

Solvents: A) neat reagent, B) pyridine, C) toluene-pyridine, pyridine equimolar to formate, D) toluene-dimethylformamide, 10: 1, E) toluene.

Alkylations with cyanoformates and chloroformates with selected alkyl groups were performed in toluene or without solvent and in pyridine or toluene-pyridine mixture(with chloroformates), at various temperatures (20°-100°C) and reagent ratios (equimolar to 30 fold excess) in good overall yields (Table). Isomeric products were separated by flash chromatography on silica gel. The reactions take place much faster with silylated or stannylated derivatives of tetrazoles than with the unsubstituted ones. The rates do not depend upon the ester function of the appropriate formate. No arylation with phenyl chloroformate was found.

As to the Table, all reactions occur in favour of N2-alkylations: with chloroformates from 1.3/1 to 7.6/1 N2/N1 ratio and with cyanoformates up to 38/1. The rate determining step of this reaction is probably the displacement of N-TMS or N-TBSn function with an alkoxycarbonyl group or the acylation of the adjacent nitrogens to the unstable intermediate (the corresponding urethane[11]), which rearranges with a simultaneous loss of carbon dioxide into 2 and 3. The lesser reactivity of cyanoformates can probably induce acylation on position N1 (Huisgen *et al.*[12] has reported on the acylation properties of cyanoformates) with subsequent rearrangement to predominant 3[13]. This thermally and/or catalytically induced decarboxylative alkylations may take place through a favourable 5-membered ring cyclic transition state mechanism involving alkyl-oxygen cleavage, which is very similar to that proposed by Vida[7]. Highly regioselective alkylation with cyanoformates on 5-phenyltetrazole and the exclusive formation of 1,3,4-oxadiazoles with phenyl, secondary and tertiary alkyl chloroformates further supports the proposed mechanism.

The reaction was extended to the s-triazolo system. Thus, silylated 3,5-dimethyl-1,2,4-triazole, was treated with benzyl chloroformate to yield merely 1-benzylated product (70%) a known compound[14].

Experimental. *Illustrative alkylation procedures are given: Preparation of 1-ethyl and 2-ethyl-5-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)tetrazole 2 and 3. Method A:* A silylated derivative of 1 (R=2',3',5'-tri-O-benzoyl-β-D-ribofuranosy, $R_1 = SiMe_3$), (1.3 g, 2.5 mmoles) was prepared in 10 ml of bis(trimethylsilyl)amine (HMDS) with stirring at reflux for 24 hours. HMDS was removed *in vacuo* and the residue stirred with ethyl cyanoformate (5 ml, 52 mmoles) at 75°C for 18 hours. The reagent was removed *in vacuo* and the residue separated by flash chromatography on silica gel with $CHCl_3$ as eluent to yield 0.75 g (55%) of 3 (R_2=Et), m.p.99°C (methanol) and 0.15 g (11%) of 2 (R_2=Et), m.p.125°C (methanol). *Method B*: A silylated derivative of 1, prepared as above was dissolved in dry toluene (5 ml), then dry pyridine (0.4 ml, 5 mmoles) and ethyl chloroformate (0.48 ml, 5 mmoles) were added. The reaction mixture was stirred at reflux for 24 hours. Pyridine hydrochloride which had separated was filtered off, the filtrate evaporated, the residue partitioned between ethyl acetate and water and the organic layer washed with dil. HCl , sat.aq. $NaHCO_3$ and brine. The products 2 (25%) and 3 (54%) after chromatography were identical to the products obtained by method A. The isomeric structures and isomeric ratios were determined from ^{1}H- and ^{13}C-NMR data. Carbon chemical shifts of N2-alkyl(Cα) as well as C5 of 3 are shifted significantly downfield as do N1-alkyl(Cα) and C5 of 2 to the opposite direction in comparison to the unsubstituted system[15,16].

2 (R=2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl, R_2=Et); M.S.: m/z=542(M^+); Calc. for $C_{29}H_{26}N_4O_7$; ^{13}C-NMR($CDCl_3$): δ=12.2($\underline{C}H_3CH_2$), 43.2($CH_3\underline{C}H_2$), 63.2(C5'); 72.0(C3'); 73.6(C1'); 74.6(C2'); 81.2(C4'); 128.5, 129.5, 129.8, 133.3, 133.5(Ph), 151.3(C5), 165.2,166.1(CO) ppm.
3 (R=2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl, R_2=Et); M.S.: m/z=542(M^+), Calc. for $C_{29}H_{26}N_4O_7$; ^{13}C-NMR($CDCl_3$): δ=14.3($\underline{C}H_3CH_2$); 48.5($CH_3\underline{C}H_2$); 64.0(C5'); 72.7(C3'); 75.2 (C2'); 75.5(C1'); 80.3(C4'); 128.4, 129.8, 133.0, 133.5(Ph); 163.6(C5); 165.1, 166.2(CO) ppm.

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