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PRENYLATION OF OLEFINS IN NITROMETHANE

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Abstract - *The prenylation of isopentenyl and 3,3-dimethylallyl derivatives could be achieved efficiently with dimethyl vinyl carbinol and a variety of acids in nitromethane. Geraniol and isopentenylacetate led to farnesyl derivatives.*

In a preceding paper[1], the reaction of various isopentenyl (IP) and 3,3-dimethylallyl (DMA) derivatives with dimethyl vinyl carbinol (DMVC) and trifluoroacetic acid (TFA) in dichloromethane was described. Compounds with the geranyl skeleton were formed in fair yields. The efficiency of the prenylation reaction was limited on the one hand by the reactivity of the prenylation product itself towards further prenylation which forced to keep the conversion low to moderate. This could be improved by the use of more reactive IP and DMA derivatives. Another side reaction was the formation of prenyl trifluoroacetate 5 which is unable to prenylate the isopentenyl derivative under the reaction conditions used.

We therefore tried to use, instead of TFA, other acids which would not give stable prenyl derivatives. Methanesulfonic acid, trifluoromethanesulfonic acid and tetrafluoroboric acid (Et_2O complex) were tried in dichloromethane and found even less efficient than TFA.

We next turned to other solvents. Nitromethane led to a substantial improvement in the conversion of IPA 1, Z=Ac. The yield of 3, Z=Ac (with time) went through a maximum owing to its further prenylation. Increasing the ratio IPA/DMVC from 0.5 to 4 improved the selectivity from 33 to 90% (entries 1 to 3). The reaction was much slower but with a longer reaction time (entries 4-6, a 85% selectivity could be achieved at about 90% conversion, Table 1) ; apparently a more dissociating solvent gave more electrophilic prenyl species.

A few other acids were next tried. Trichloroacetic acid was a little less efficient (entries 7-10) but very selective ; phosphoric (entries 11-13) and conc. sulfuric acid (entries 18-21) were a little less good perhaps owing to their limited solubility in nitromethane. Methanesulfonic acid proved extremely good, fluorosulfonic acid giving very similar results (entries 14-17 and 22-25 respectively).

Prenyl acetate could also be prenylated efficiently with DMVC and TFA at 0° in nitromethane. The results are shown in Table 2. Yields of over 80% were obtained at about 80% conversion.

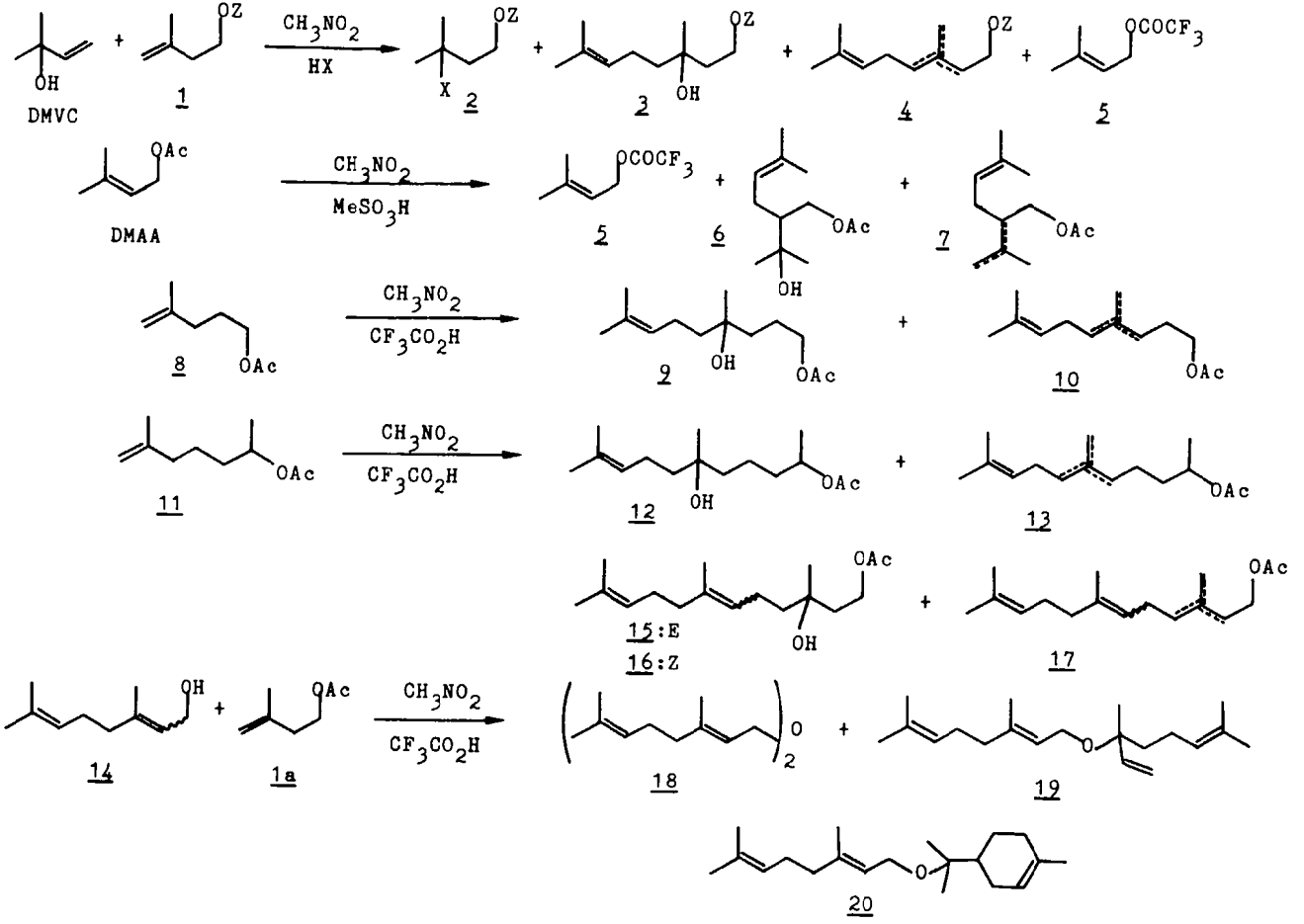
DMVC
1
2
3
4
5
DMAA
6
7
8
9
10
11
12
13
15:E
16:Z
17
14
1a
18
19
20

Table 1 - Prenylation of IPA at 0°C in nitromethane (2.5ml) with DMVC and various acids

Entry	Time mn	IPA mmol	DMVC mmol	$MeNO_2$ ml	TFA mmol	Conv. DMVC %	Conv. IPA %	5 %	3 Z=Ac %	4 Z=Ac %	Total prenylation %
1	20	0.5	1	2.5	2.6	90	62	27	30(33)[a]		(33)
2	20	2.5	"	"	"	76	67	11	55(72)	2	(72)
3	20	4	"	"	"	44	44	0.8	39(91)	3	(95)
4	10	"	"	"	"	24	24	0.4	22	2	(100)
5	40	"	"	"	"	66	54	1.2	55	5	(92)
6	90	"	"	"	"	95	87	1.6	73	7	(85)
						CCl_3COOH					
7	10	4	1	2.5	3	13	12		12	0	(92)
8	20	"	"	"	"	26	24		24	0	(92)
9	40	"	"	"	"	45	41		40	1	(91)
10	90	"	"	"	"	71	64		61	2	(89)
						H_3PO_4 (90%)					
11	20	4	1	2.5	3	15		12	0	(60)	
12	90					70	63		45	8	(76)
13	150					85	66		46	9	(65)
						$MeSO_3H$					
14	10	4	1	2.5	0.3	20	20		17	3	(100)
15	20	"	"	"	"	32	32		25	4	(91)
16	40	"	"	"	"	49	48		39	6	(92)
17	90	"	"	"	"	70	64		32	8	(86)
						H_2SO_4					
18	10	4	1	2.5	0.2	67	62		45	6	(76)
19	20	"	"	"	"	82	72		57	7	(78)
20	40	"	"	"	"	94	80		62	8	(75)
20	90	"	"	"	"	100	84		66	8	(74)
						FSO_3H					
22	10	4	1	2.5	0.1	49	40		32	5	(76)
23	20	"	"	"	"	69	64		48	7	(82)
24	40	"	"	"	"	80	72		57	8	(83)
25	90	"	"	"	"	88	80		63	9	(82)

a) in parentheses : yield calculated on converted DMVC

Table 2 -Prenylation of DMAA (4mmol) with DMVC(1mmol) and CF_3COOH(2.6mmol)in $MeNO_2$(2.5ml) at 0°

Entry	Time (mn)	Conv. DMVC %	Conv. DMAA %	5 %	6 %	7 %	Total prenylation
1	10	20	19	0.8	19	0	(95)
2	20	43	41	1	37	2	(91)
3	40	56	53	1.5	47	3	(89)
4	90	85	7	2	67	4	(84)

The acetate 8, homolog of 1, was also submitted to these reaction conditions (90min). Compounds 9 and 10 were obtained in yields (29 and 39%) much higher than in dichloromethane[1]. Similarly the next homolog 11 gave 12 and 13 in 28 and 42% yield respectively. It is to be noted that under these conditions no addition of TFA to 8 or 11 seemed to take place.

Various derivatives of isopentenol were also treated under the above conditions, as shown in Table 3. As in our previous work[1] the fluorinated ethers were very much more reactive than the acetate or the n-butyl ether. The differences are however smaller and with the less reactive substrates, the reaction could be allowed to proceed longer with no damage as it is very clean.

Table 3 - Prenylation of ether 1 (4mmol) with DMVC (1mmol) and TFA (2.6mmol) in $MeNO_2$ (2.5mmol) for 20mn at 0°

1	Z=	Conversion		3 %	4 %	Total
		DMVC %	1 %			Prenylation
a	Ac	44	44	39	3	(95)
b	Bu	36	35	19	15	(94)
c	CF_2-CClFH	95	77	63	12	(79)
d	CH_2-CF_3	95	78	57	16	(77)

The progress made in the efficiency of the prenylation conditions was checked in a preparative experiment carried out with IPA (0.4mol) and DMVC (0.1mol) with $MeSO_3H$ (0.03mol) as catalyst. After 90mn at 0° the unchanged reagents (mainly IPA) were recovered by distillation and engaged in another run. After 3 such cycles compounds 3, Z=Ac and 4, Z=Ac were isolated by distillation in yields of 61% and 11% respectively. It has been shown that oxidation of the alcohols 3, Z=H or 4, Z=H can lead under prototropy to citral [2,3].

A similar preparative experiment with prenylacetate (DMAA) led to 6 (50%) and 7 (9%). Dehydration of 6 to lavandulyl acetate was carried out with phosphorus oxychloride in pyridine (94%).

The above results encouraged us to try a biomimetic synthesis of farnesyl derivatives. The geranylation of IPA derived substrates has met so far with limited success[2,4,5,6]. The main side reactions observed were cyclisation to terpineol and addition of acids to the remote double bond Some cases are however known where nucleophilic aromatic substrates such as olivetol[7] or 1,3,5-trimethoxybenzene[8] are efficiently geranylated. Comparative experiments with geraniol and nerol showed nearly complete retention of configuration, in agreement with previous work on the stereochemistry of allylic carbocations[9].

In fact when geraniol was treated with IPA (4eq) and sulfuric acid in nitromethane at 0° the glycol monoacetate 15 was isolated in a yield of 15%. Also formed were some of the Z isomer 16 and the triene ester 17 (5%). Some linalool and terpineol were detected together with cyclic C_{10} hydrocarbons. Other byproducts were geranyl geranyl ether 18 and, probably, geranyl linalyl ether 19 and geranyl -terpinyl ether 20 ; the formation of these is probably due to the quenching of the geranyl electrophile (ion pair ?) by the various alcohols present in the reaction medium. Keeping the concentration of geraniol very low (by adding it very slowly) led to an increase in the yield of C_{15} compounds. Further improvement was observed when TFA was used instead of sulfuric acid. The glc yield of 15-17 was 57% and a preparative run gave 15 in an isolated yield of 45%.

With nerol itself the reaction was less efficient (20% total) but the main compound was the Z derivative 6. It is remarkable that the nerylation of isopentenyl acetate should be able to compete with the well known facile cyclization. Linalool gave intermediate results, Table 4.

Table 4- Condensation of C_{10} alcohols (1eq.) with IPA (4eq.) in $MeNO_2$ at 0°C

	Conversion C_{10}alcohol %	15%	16%	17%	Terpineol %	Linalool %	18+19+20 %	C10 HC%	Total geranylation
1. Geraniol 2h, H_2SO_4 (0.2eq.)	90	15		5	10	8	14	11	20
2. Geraniol[a] 4h, H_2SO_4 (0.2eq.)	95	25	3	10	15	5	6	9	38
3. Geraniol[a] 2h, TFA (2.6eq.)	95	45	4	8	7	-	4	3	57
4. Nerola 1h, TFA (2.6eq.)	96	3	11	6	33	-	4	12	20
5. Linalool[a] 1h, TFA (2.6eq.)	100	31	8	7	14	-	5	8	46

a/ slow addition

This technique could be applied to the geranylation of 1,2-dimethoxy benzene (57%).

EXPERIMENTAL

Commercial solvents were dried over $CaCl_2$ and distilled from CaH_2, P_2O_5 or benzophenone radical anion. Glc analyses were carried out on a Girdel 30 apparatus equipped with an apolar column (OV101, 10% on chromosorb WHP ; 100-120 mesh, 3m) or with a capilary glass column (SE52, 25m x 0,6mm). Dodecyl acetate was used as internal standard ; integrations were carried out with an Intersmat Minigrator.

^1H NMR spectra were recorded in $CDCl_3$ (in ppm with respect to T.M.S.) on a Cameca 250. ^{13}C spectra were recorded on a Bruker WH90 machine. IR spectra were recorded ($CHCl_3$) with a Perkin Elmer 599 apparatus. Glc-mass analyses were carried out on a Riber R-10-10 apparatus equipped with a capillary column SE 52. HPLC analyses were carried out on a Dupont 850 apparatus using a Zorbaxsil B 1500 column. Preparative MPLC was executed on Merck Lobar columns. Combustion analyses were carried out by the Analytical Laboratory of the University P. & M. Curie to whow we express our gratitude.
Compounds 1-13 were described in a previous paper[1]. An authentic sample of 17 was obtained by dehydration (POCl3/pyridine) of the corresponding tertiary alcohol 15. Compounds 19 and 20 were obtained as a mixture and were identified by their NMR and glc-mass spectra. Yields in brackets take into account the recovered starting material.

CONDENSATION OF IPA 1, Z=Ac, WITH DMVC

To the IP derivative (4mmol), DMVC (1mmol) and n-heptyl acetate (130mg) in nitromethane, the acid was rapidly added with stirring at 0°, either neat or as a 2M solution in nitromethane. Aliquots were removed at the indicated times quenched with aqueous saturated sodium bicarbonate (0.5ml) and ether (0.5ml) and the organic phase analysed by glc.

PREPARATIVE RUN

a/ 1-Acetoxy-3,7-dimethyl-6-octen-3-ol 3, Z=Ac :
To a mixture of IPA (51.2g, 0.4mol), DMVC (8.6g, 0.1mol) in nitromethane (250ml) cooled to 0°, methanesulfonic acid (2ml, 31mmol) was gradually added with stirring. After 90mn excess aq. sodium bicarbonate was added and the mixture extracted with ether 3 times. After the usual work up the solvents and excess IPA were removed by distillation i.v. (272g) and treated again with IPA (12.8g), DMVC (8.6g) and methanesulfonic acid (2ml). After three such cycles the distillation residues were distilled together (0.1mmHg). After a forerun (3g) t 70°, a diene fraction 4, Z=Ac (6g, 11%) was collected at 70-100° ; its composition was

ascertained by glc comparison with references samples (exo : 27%, 3E : 30%, 3Z : 15%, 2E : 19%, 2Z : 9%). The diol monoacetate 3, Z=Ac was collected (39g, 61%) at 115- 120°.

b/ 2,6-Dimethyl-3-acetoxymethyl-5-hepten-2-ol, 6 :

A similar run with prenyl acetate and DMVC gave a forerun t 75° (4g), a fraction bp 75-105° containing lavandulyl (75%) and isolavanderlyl (25%) acetates (5.3g, 9%) ; the main fraction, bp 110-115° (32g, 50%) was 90% pure diol acetate 6.

Lavandulyl acetates

Phosphorus oxychloride (1.4ml, 1.5eq) was added to the diol acetate 6 (2.14g) in pyridine (30ml) at 0° and the mixture allowed to stand overnight at room temperature. After the usual work up distillation gave a colourless oil (1.84g, 94%) containing lavandulyl (95%) and isolavandulyl (5%) acetates.

GERANYLATION OF IPA

A solution of geraniol (7.7g, 0.05mol) in nitromethane (30ml) was added at 0° with stirring to IPA (25.5g, 0.2mmol) and TFA (10ml) in nitromethane (125ml). After two hours the mixture was poured in to excess aqueous saturated HCO_3Na and extracted (3x) with ether. The solvent and excess IPA were removed i.v. and the residue chromatographed on silicagel (the fractions being analysed by glc). Elution with petroleum ether mixture (95/5 gradually enriched until 0/100) gave successively geranyl ethers 18 (mainly), 19 and 20[10] (0.25g), trienesters 17 (1.25g), terpineol and 16 (0.90g) and finally 15 (4.7g), various fractions contained unidentified products (1.2g).

Digeranyl ether, 18 :

^1H NMR(90MHz) : 5.4(2H,t) ; 5.12(2H,t) ; 3.98(4H,d,J=6.6Hz) ; 2.07(8H,m) ; 1.72(12H,s) ; 1.62(6H,s).

3,7,11-Trimethyl-3-hydroxy-6,10-dodecadien-1-yl acetate, 15 :

IR($CHCl_3$) : 3590(f), 3470(f), 2965(m), 2920(m) 2850(m), 1730(F), 1370(m), 1240(F), 1110(m) and 1035(m). ^1H NMR(250MHz) : 5.11(2H,m) ; 4.24(2H,t,J=7Hz) ; 2.05(3H,s) ; 2.14- 1.95(6H,m) ; 1.82(2H,dt,J_1=7Hz,J_2=1Hz) ; 1,67(3H,s) ; 1.62(3H,s) ; 1.59(3H,s) ; 1.57-1.47(2H,m) ; 1.22(3H,s).

^{13}C NMR (80MHz) : 170.7(Ac) ; 135.2(C=) ; 131.1(C=) ; 124.0(-CH=) ; 123.7(-CH=) ; 71.8(C-OH); 61,3(OCH_2) ; 42.2(CH_2) ; 39.8($2CH_2$) ; 27.0(CH_3) ; 26.7(CH_2) ; 25.8(CH_3) ; 22.7(CH_2) ; 21.2(Ac) ; 17.8(CH_3) ; 16.1(CH_3).

m/e : 264($M-H_2O$,2.5%), 204(1), 189(1), 177(2), 161(6), 142(2), 148(1), 147(1), 136(12), 135(19), 123(11), 121(15), 109(7), 107(34), 105(6), 95(10), 93(66), 91(12), 81(32), 79(20), 77(10), 71(42), 69(100), 67(29).

$C_{17}H_{30}O_3$

GERANYLATION OF 1,4-DIMETHOXY BENZENE.

2-(3,7-Dimethyl-2,6-octadien-1-yl) 1,4-dimethoxybenzene :

To a solution of 1,4-dimethoxybenzene (13.8g,0.1mol) in nitromethane (50ml) were successively added at 0° a solution of sulfuric acid in nitromethane (2M, 3ml) and gradually, in 30mn, a solution of geraniol (3.1g, 0.02mol) in nitromethane (100ml). After 2.5h the reaction mixture was quenched with saturated aqueous sodium bicarbonate and worked up as usual. After distillation i.v. of excess dimethoxybenzene, the residue was chromatographed to give 1-geranyl-2,5--dimethoxy benzene (3.11g, 57%) containing 5-7% of the Z isomer.

^1H NMR(90MHz) : 6.83-6.58(3H,m) ; 5.28(1H,t) ; 5.09(1H,t) ; 3.73(3H,s) ; 3.69(3H,s) ; 3.29(2H,d,J=7Hz) ; 2.04(4H,s) ; 1.67(6H,s) ; 1.58(3H,s).

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