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Methyleniminium Salts as Acylating Agent - One Step Synthesis of Baccatin III from 10-Deacetylbaccatin III with High Selectivity

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Dedicated to Prof. G. KIRSCH on the occasion of his 50th birthday

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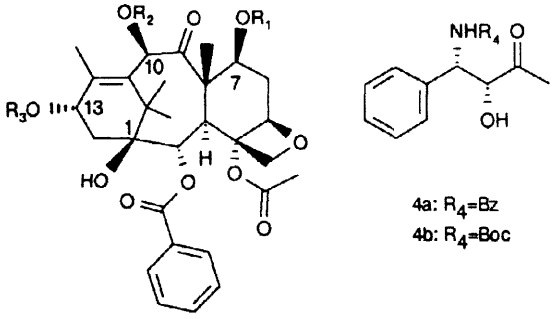
Abstract

New methyleniminium salts were investigated as acylating agent of 10-deacetylbaccatin III. Thus, synthesis of baccatin III was performed in one step with 79% isolated yield and 98% selectivity using the iminium salt prepared from mesyl chloride and N-ethylacetamide.

Keywords: *Iminium salts* *Acylation* *Regioselection* *Taxoids*

Baccatin III **2** (Scheme 1) like its biosynthetic precursor 10-deacetylbaccatin III (10-DAB) **1** is a natural taxane extracted from yew species (genus *Taxus*)[1]. As 10-DAB **1** was found to be the most abundant taxane in yew leaves of *Taxus baccata* L.[2], baccatine III received much less interest as natural precursor for large-scale hemisynthesis of taxoids, a new class of antitumor agents whose marketed representatives are paclitaxel **3** (Taxol®) and docetaxel **4** (Taxotere®)[3]. Much more used is the C-7 O-triethylsilyl derivative **5** of baccatin III, obtained from 10-DAB **1** by selective protection of C-7 hydroxyl group with chlorotriethylsilane followed by selective acetylation at C-10 position[4], which is a key intermediate for synthesis of paclitaxel and analogues[5] as well as for preparation of baccatin III itself by desilylating **5** with trifluoroacetic acid[6].



4a: R_4=Bz
4b: R_4=Boc

1	R_1=H,	R_2= H,	R_3=H	**7**	R_1=Ac,	R_2=Ac,	R_3=Ac
2	R_1=H,	R_2= Ac,	R_3=H	**8**	R_1=H,	R_2=Ac,	R_3=Ac
3	R_1=H,	R_2= Ac,	R_3=4a	**9**	R_1=Ac,	R_2=Ac,	R_3=H
4	R_1=H,	R2= H,	R_3=4b	**10**	R_1=Ac,	R_2=H,	R_3=Ac
5	R_1=Si(Et)$_3$,	R_2=Ac,	R_3=H	**11**	R_1=Ac,	R_2=H,	R_3=H
6	R_1=H,	R_2=CHO,	R_3=H	**12**	R_1=H,	R_2=H,	R_3=Ac

Scheme 1

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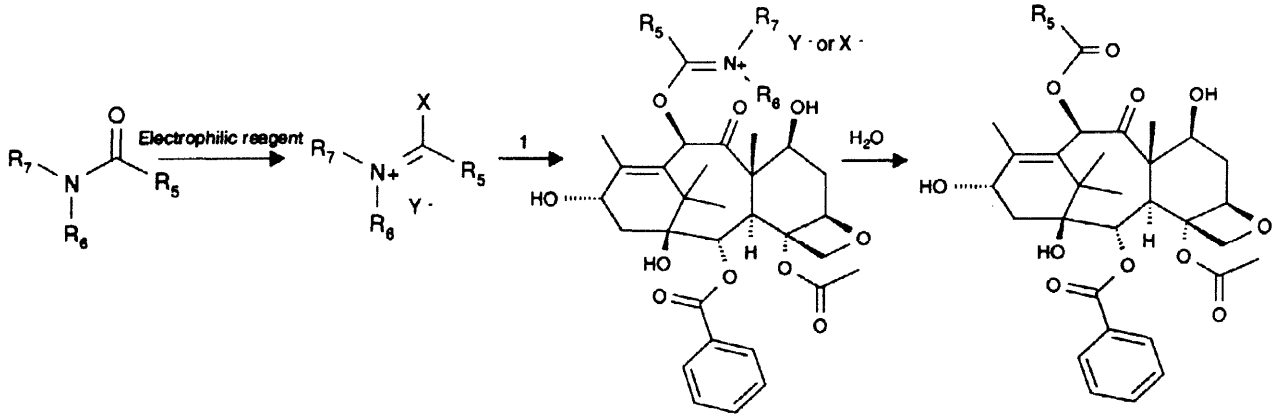
As attempts to prepare baccatin III by chemical[7] or biochemical[8] acetylation of **1** resulted in low yield and/or low selectivity, we investigated new acetylating agents for the purpose.
Use of methyleniminium salts as acylating agent of hydroxylated compounds is well known in the litterature but is mainly limited to O-formylation[9]. One report mentions the use of chloromethyleniminium chlorides for propionylation and benzoylation of ethanol and phenol with dialkylbenzamide and dialkylpropionamide[10]. Here we report the use of new methyleniminium salts for both formylation and acetylation of the tetraol **1** with high selectivity (Scheme 2).



Scheme 2

Formylation of 10-DAB **1** (Table 1, entry 1) has been performed with the adduct generated *in situ* from triflic anhydride and dimethylformamide[11] at -20°C in presence of the substrate. No triflated derivatives of **1** were detected by HPLC, indicating rapid consumption of the anhydride by the amide in excess (solvent).

Table I: Acylation of 1

Entry	Amide	Eq.	Electrophilic reagent	Eq.	Reaction conditions	Hydrolysis conditions	Yield
1	R_5= H, R_6= R_7= Me	29	$(CF_3SO)_2O$	1.2	1, -20°C, 10 min.	H_2O, 3h., 0°C	6: 90%[a]
2	R_5= Me, R_6= Et, R_7=H	35	CH_3SO_2Cl	5.1	17h., 0°C then 1, 0°C, 30h.	AcONa aq. (6.2éq.), 25h., 20°C	2:79%[a]
3	R_5= Me, R_6= R_7= Et	36	$(p\text{-}CH_3\text{-}Ph\text{-}SO_2)_2O$	5.0	DCE , 0°C, 35 min., then 1, 4h30, 20°C	CH_3CN, H_2O, 5 min.,20°C	2:66%[b]
4	R_5= R_6= Me, R_7= H	59	ClCOCOCl	5.1	DCE , 0°C, 25 min., then 1, 0°C, 19h	AcONa aq. (6.2éq.), 24h., 20°C	2:40%[b]
5	R_5= R_6= Me, R_7= H	57	ClCOCOCl	10.0	DCE , -15°C, 60 min., then 1, -15°C, 16h30	NaHCO3 aq. (17éq.), 4h., 20°C	2:75%[b]
6	R_5= R_6= Et, R_7= H	47	$POCl_3$	5.1	DCE , 20°C , 15 min. then 1, 20°C, 3h	CH_3CN, H_2O, 5 min., 20°C	2:22%[b]
7	R_5= R_6= Me, R_7= H	59	$p\text{-}CH_3\text{-}Ph\text{-}SO_2Cl$	5.2	CH_3CN , 20min., 20°C, then 1,17h, 20°C	AcONa aq. (6.2éq.), 24h., 20°C	2:16%[b]
8	R_5= R_6= Me, R_7= H	58	$(CF_3SO)_2O$	2.8	DCE, 0°C, 1h., then 1, 0°C, 17h	AcONa aq. (6.2éq.), 24h., 20°C	2: 6%[b]

a: isolated yield ; b: reaction yield determined by external standardization in CLHP; DCE: 1,2-dichloroethane

Due to the high reactivity of the corresponding sulphonyloxyiminium salt, reaction was completed within 10 minutes and selectivity for C-10 hydroxyl was found to be higher than 95% by HPLC (around 2.5% of a di-formylated derivative and 0.9% of a mono-formylated derivative were detected by HPLC in the medium). Hydrolysis of the baccatin iminium salt

was made by addition of water to the medium resulting in precipitation of the expected product with an excellent yield[1].

Acetylation of **1** was attempted with various iminium salts prepared from N-alkyl or N,N-dialkylacetamide and electrophilic reagent (Table I, entries 2 to 8). As previously, a large excess of amide was used in order to minimize side reaction of unreacted electrophilic reagent with the substrate. By contrast with formylation, acetylation procedures began with previous preparation of the adducts at temperature ranging from -20°C to room temperature within 30 to 80 minutes. With N-ethylacetamide and mesyl chlorid (entry 2), preparation of the adduct is described by keeping the medium at 0°C for 17 hours[2] but a one hour contact was found to have no consequence on reaction kinetic and yield.

Preparation of iminium derived from N-ethylacetamide and oxalyl chloride was achieved within five minutes at 0°C as indicated by gas release but competitive formation of N,N'-diacetyl-N,N'-diethyl-oxalamide[13] was observed by HPLC resulting in undesirable consumption of the reagents (entry 4). This side reaction has been minimized using a higher amount of oxalyl chlorid and performing both iminium preparation and reaction at -15°C, as shown by improvment of the reaction yield (entry 5).

In most cases, reaction of tetraol **1** with iminium salts were not complete, even after long reaction times (entry 5 to 8). The use of triflic anhydride or p-toluenesulfonyl chlorid with N-methylacetamide gave furthermore significant side reactions resulting in poor yields of **2** (entries 7 and 8). Completion was reached after a few hours at room temperature with the adduct from N,N-diethylacetamide and p-toluenesulfonic anhydride (entry 3) and after 25 hours at 20°C with the adduct from N-ethylacetamide and mesyl chlorid (entry 2).

Hydrolysis of baccatin iminiums were carried out by quenching the medium with water or an aqueous solution of a base in such a way to keep acidic the medium. When a N-monoalkyl acetamide was used, hydrolysis was kinetically controled by disappearance of the free imine which is in equilibrium with the protonated form. Therefore, a limitation is the extraction of the imine in the organic phase when hydrolysis is performed in biphasic conditions. In the case of the adduct prepared from phosphorus oxychloride and N-methylacetamide, the N-methyl imine of baccatine III was found to be the major component by HPLC after contact with water-

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[1] Preparation of **6**: In a 50 ml flask, fitted with a thermometer , a stirrer and a dropping funnel, are placed under nitrogen 12 ml of N,N-dimethylformamide (155mmol), 0.495 ml pyridine (6.1 mmol) and 3g of 10-DAB (5.4 mmol). After cooling to -20°C with a dry ice-acetone bath , triflic anhydride (1.08 ml, 6.4 mmol) is dropped within 10 minutes with a seringue to the reaction medium which is further stirred for 10 minutes at -20°C and hydrolysed with 60 ml of water. After being maintained for 3 hours at 0°C with an ice-water bath, the resulting suspension is filtered and dried overnight under reduced pressure. 2,87g of a white solid are obtained (97% purity by normalized pic area in CLHP, 90% yield). ^{1}H N.M.R. (400 MHz, $CDCl_3$, δ in ppm) : 1.11 (s, 3H : CH_3) ; 1.13 (s, 3H : CH_3) ; 1.69 (s, 1H : OH en 1) ; 1.71 (s, 3H : CH_3) ; 1.87 and 2.58 (2 m, 1H each : CH_2 6) ; 2.08 (s, 3H : CH_3) ; 2.18 (d, J = 5 Hz, 1H : OH in 13) ; 2.25 (d, J = 5 Hz, 1H : OH in 7) ; 2.29 (s, 3H : $COCH_3$) ; 2.32 (d, J = 9 Hz, 2H : CH_2 14) ; 3.91 (d, J = 7 Hz, 1H : H 3) ; 4.16 and 4.33 (2 d, J = 8.5 Hz, 1H each : CH_2 20) ; 4.47 (m , 1H : H 7) ; 4.91 (m, 1H : H 13) ; 5.00 (broad d, J = 10 Hz, 1H : H 5) ; 5.64 (d, J = 7 Hz, 1H : H 2) ; 6.46 (s, 1H : H 10) ; 7.00 (t, J = 7.5 Hz, 2H : $OCOC_6H_5$ H meta) ; 7.64 (t, J = 7.5 Hz, 1H : $OCOC_6H_5$ H para) ; 8.13 (d, J = 7,5 Hz, 2H : $OCOC_6H_5$ H ortho) ; 8.23 (s, 1H : OCOH). IR (KBr) : 3622, 3517, 3400, 3061, 3019, 2990 to 2850, 1739, 1715, 1704, 1271, 1250, 1156, 1100 to 1000, 977, 719. MS (NH_3) M/Z 590 $(M+NH_4)^+$, 573 $(M+H)^+$, 544 , 527; $[\alpha]^{20}_D$ = -60 ± 1 (c = 0.5, acetone).

[2] Preparation of **2**: In a 250 ml reactor, fitted with a thermometer , a stirrer and a dropping funnel, are placed under nitrogen 60 ml of N-ethylacetamide (627mmol). After cooling to -20°C, mesyl chlorid (7.2ml, 92 mmol) is dropped within 15 minutes with a seringue and the reaction medium is maintained for 30 minutes at -20°C and then for 17 hours at 0°C. 10g of 10-DAB III (17,9 mmol) are charged into the reactor and the suspension is stirred for 30 hours at 0°C. After transfer into a 1 liter reactor, a solution of 15g of sodium acetate trihydrate (110 mmol) in 300 ml water is added within 45 minutes and the resulting solution maintained 25 hours at 20°C. The suspension is filtered and the solid is washed three times with 50 ml water. After drying overnight at 50°C, 9,0g of baccatin III are obtained (92% purity by external standardization in CLHP, 79% yield). ^{1}H NMR, IR and mass spectra are consistent with the structure.

acetonitrile (HPLC eluent) for a few minutes (entry 6, reaction yield underestimated). With N-ethylacetamide and mesylchlorid, hydrolysis at pH=2 was stopped after 30 hours at 0°C, at which stage the N-ethyl imine of baccatin III representated around 5% in area percent by HPLC.

Selectivity of the acetylation was investigated in detail when optimal conditions were used (entry 2). All acetylated derivatives **7-12** of tetraol **1** relative to C-7,C-10 and C-13 positions were prepared and identified by HPLC (Figure 1). Analysis of the hydrolysed medium allowed to detect less than 1% of the C-7 O-acetyl, C-7,C-10 O-diacetyl derivatives **11** and **9** and less than 0.5% of the C-10,C-13 O-diacetyl derivative **8** (selectivity higher than 98%).

In conclusion, we demonstrated that methyleneiminium salts represents an useful alternative for acylation of substrates where classical reagents do not suit and that baccatin III can be easily prepared from 10-DAB in one step with high yield and selectivity.

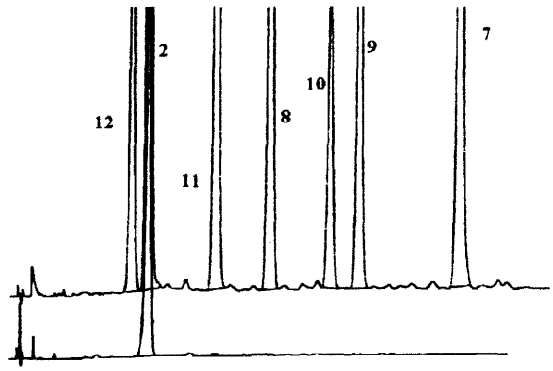

Figure 1: Chromatogram from the reaction of 1 with N-ethylacetamide and mesyl chlorid adduct[3].

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[3] HPLC analysis were performed on a Kromasil C_{18} bonded phase 5 µm using an elution gradient with water-acetonitrile.