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Allylic Substitution / Rearrangement of Cannabinoids with Trimethylsilyl Bromide

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Key Words: Trimethylsilyl bromide, allylic acetate, bromide, substitution, rearrangement, cannabinoids.

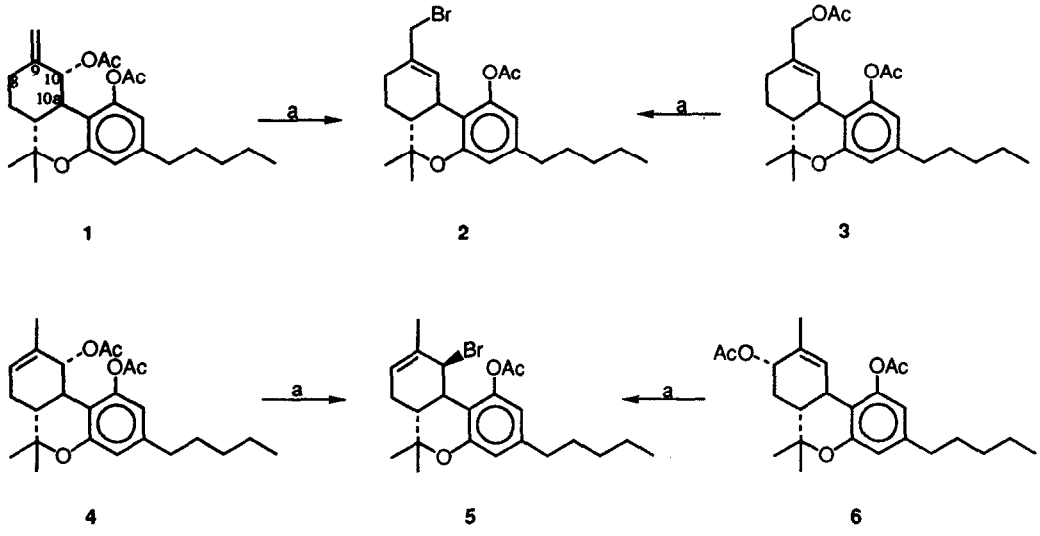
Abstract: *Trimethylsilyl bromide (TMSBr) in the presence of catalytic ZnI_2 induces facile substitution of allylic acetates to the bromides with or without rearrangement as governed by product stability. This was applied to the preparation of a key intermediate employed in the synthesis of important cannabinoid metabolites.*

The synthesis of metabolites of Δ^9-tetrahydrocannabinol, the active constituent of marihuana, continues to be of interest.[1-4] Of special interest is the synthesis of the urinary metabolite 9-carboxy-11-nor-Δ^9-THC which, as the analyte assayed for in drug abuse testing for marihuana use, is sought as the analytical standard in forensic testing. The method most frequently used to prepare the carboxy metabolite utilizes 11-bromo-Δ^9-THC acetate (2) as a key intermediate.[5] The formation of 2 from the allylic acetate 1 with HBr in acetic acid affords a mixture of products that is used without chromatographic purification and results in an overall low yield after subsequent acetolysis and hydrolysis.[5] Since the 11-hydroxy and 9-carboxy metabolites that can be obtained via 2 are in continuing need, an improved transformation of 1 to 2 was sought that would afford a more homogeneous product and thus improve the yield of subsequent steps and reduce purification problems.

Trimethylsilyl bromide was examined as the reagent even though its reaction with esters has been reported to be a poor process.[6] The salient difference suggesting its utility here was that the allylic system should facilitate a process that proceeded by an S_n1 mechanism. The mechanism of the related trimethylsilyl iodide dealkylation of esters to afford the alkyl halides has been described as either an S_n2 or S_n1 process depending on the alkyl group.[7]

Treatment of 10α-acetoxy-$\Delta^{9,11}$-THC (1) with 5 eq. of TMSBr at reflux for 48 h afforded a 61% chromatographed yield of the rearranged allylic bromide 2. In some experiments a significant proportion of starting acetate was recovered. A more facile conversion was observed in the presence of 5 mole % of ZnI_2 as a catalyst where the reaction went to completion at ambient temperature with two to three equivalents of TMSBr within 4 h. This afforded essentially a single component in 97% yield without purification.

A series of allylic acetate isomers were similarly examined to provide some insight into the mechanism of this reaction. Acetates 3 and 4 afforded unrearranged bromides while their allylic isomers 1 and 6 respectively gave rearranged products. The observed regioselectively within the allylic isomer pairs 1/3 and 4/6 is consistent with a mechanism proceeding via a common allylic cation intermediate. The observed products were the most stable olefins. From 1/3, the trisubstituted endocyclic double bond (2) is favored over the disubstituted exocyclic double bond.[8] With 4/6, the Δ^8-double bond (5) is favored over the thermodynamically less stable Δ^9-double bond (which in the non-halogenated cannabinoids amounts to a 2.4 kcal/mole difference).[9]



1 2 3

4 5 6

a. TMSBr, ZnI_2, r.t.

In a typical procedure, the allylic acetate 1 (0.054 mol) in CH_2Cl_2 (1.1 L) was added to 0.0027 mole of anhydrous ZnI_2 followed by TMSBr (0.11 mol) with stirring under nitrogen at ambient temperature. The reaction was complete within four hours and was shaken with aqueous $NaHCO_3$, washed with brine and dried over Na_2SO_4 to afford an 97% yield of the bromide 2. NMR and tlc showed predominantly a single component which was characterized as (2) by NMR, MS and elemental analysis.[10]

Substrate	Product	Yield
1	2	97
3	2	87
4	5	79
6	5	64

These results demonstrate an improved allylic rearrangement procedure to provide an important synthetic intermediate for the preparation cannabinoid metabolites. Furthermore, these results suggest the use of TMSBr in the presence of ZnI_2 to effect a facile substitution of allylic acetates by bromide in contrast to its sluggish reaction with unactivated esters.

Acknowledgement

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10. **Compound 2:** ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.7 Hz, ϵCH_3), 1.09 (s, 3H, 6α-CH_3), 1.42 (s, 3H, 6β-CH_3), 2.29 (s, 3H, OAc), 2.50 (t, 2H, J = 7.7 Hz, α-CH_2), 3.10 (bd, 1H, J = 10.6 Hz, 10a-H), 3.94 (dd, 2H, J = 9.2 Hz, CH_2Br), 6.42 (d, 1H, J = 1.7 Hz, ArH), 6.49 (s, 1H, 10-H), 6.56 (d, 1H, J = 1.5 Hz, ArH').
HRMS Calcd. for $C_{23}H_{31}{}^{79}BrO_3$: 434.1457; Found 434.1456.
Elemental Analysis (chromatographed sample) Calcd. for $C_{23}H_{31}BrO_3$: C 63.45, H 7.18; Found C 63.85, H 7.01.
Compound 5: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.7 Hz, ϵCH_3), 1.13 (s, 3H, 6α-CH_3), 1.42 (s, 3H, 6β-CH_3), 1.88 (bs, 3H, vinyl CH_3), 2.29 (s, 3H, OAc), 2.52 (t, 2H, J = 7.8 Hz, αCH_2), 2.79 (dd, 1H, J = 3.3, 11.5 Hz, 10a-H), 5.33 (d, 1H, J = 2.9 Hz, 10α-H), 5.62 (bs, 1H, vinyl H), 6.47 (d, 1H, J = 1.6 Hz, ArH), 6.59 (d, 1H, J = 1.5 Hz, ArH[1]).
HRMS Calcd. for $C_{23}H_{31}{}^{79}BrO_3$: 434.1457; Found 434.1456.

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