A NEW SYNTHETIC METHOD OF 6-ARYL- OR VINYL-SUBSTITUTED 2-OXO-TETRAHYDRO-1,3-OXAZINES

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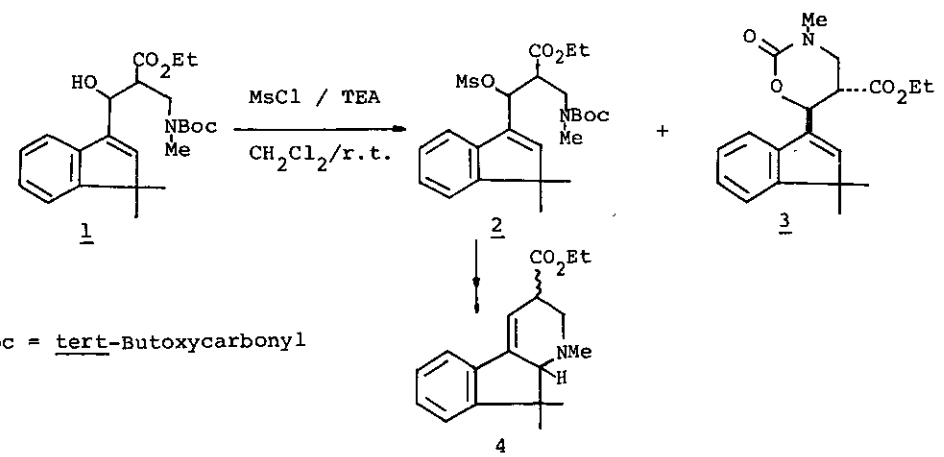
Abstract ——— A novel transformation of benzylic or allylic hydroxy-substituted N-tert-butoxycarbonyl compounds by treatment with methanesulfonyl chloride in the presence of triethylamine into 2-oxotetrahydro-1,3-oxazines is described.

Recently we have reported a synthesis of ethyl 9,9-dimethyl-1,2,3,9a-tetrahydro-9H-indeno[2,1-b]pyridine-3-carboxylate (4) via the route involving mesylation of the alcohol (1) with methanesulfonyl chloride (MsCl) in the presence of triethylamine (TEA),[1] in the process of which the formation of an unidentified cyclized compound as by-product was observed. Upon reinvestigation of this reaction, we have now established the by-product to be 2-oxotetrahydro-1,3-oxazine (oxazinone) derivative and hence introduced a new synthesis of oxazinones, which have been extensively investigated due to the interesting biological activities.[2]



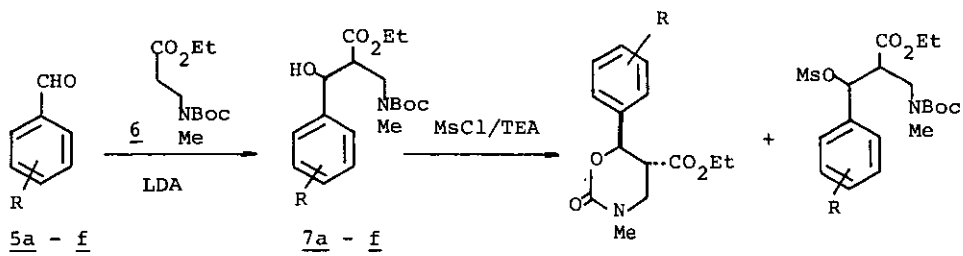
1 2 3 4

Boc = tert-Butoxycarbonyl

Mesylation of 1 and subsequent purification by column chromatography (silica gel, benzene - EtOAc, 1 : 1 v/v) afforded the by-product (3) in 27% yield. From the spectral evidences,[3] the structure of 3 was deduced as having a cyclic urethane system, oxazinone. The oxazinone cyclization from a hydroxy-substituted urethane in the presence of base or acid is well documented.[4] However it was observed that no reaction took place by treatment of 1 with TEA in the absence of MsCl. This results strongly suggested that MsCl used works effectively for the formation of 3. Based on these new findings, we investigated a general synthetic method of 2-oxotetrahydro-1,3-oxazines using simple model compounds.

Treatment of the alcohol (7a), prepared from benzaldehyde (5a) by condensation with ethyl N-tert-butoxycarbonyl-N-methylpropionate (6) in the presence of lithium diisopropylamide (LDA) in THF at -78 °C, with MsCl (1.5 eq) and TEA (3 eq) in CH_2Cl_2 at room temperature afforded the mesylate (9a) in 47% yield together with a 36% yield of a single oxazinone (8a), whose spectral properties are as follows : ir (liquid film) 1720 and 1705 cm^{-1}; ^1H nmr ($CDCl_3$) 1.05 (3H, t, J=7.3 Hz, $CO_2CH_2CH_3$), 3.06 (3H, s, NCH_3), 3.15 (1H, ddd, J=8.9, 7.8 and 5.2 Hz, 5-H_{ax}), 3.38 (1H, dd, J=11.5 and 8.9 Hz, 4-H_{eq}), 4.03 (2H, q, J=7.3 Hz, $CO_2CH_2CH_3$), 5.45 (1H, d, J=7.8 Hz, 6-H_{ax}), and 7.35 ppm (5H, m, Ar-H); MS (m/z) 263 (M^+).

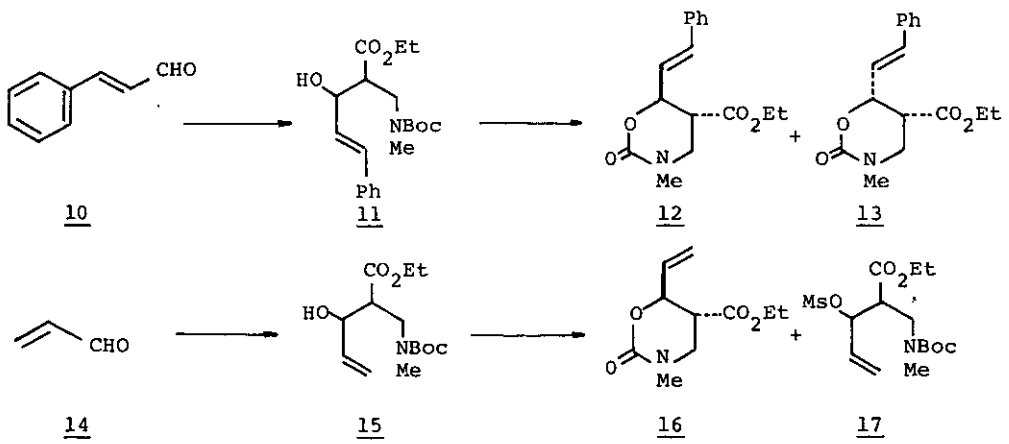
Under similar reaction conditions the benzaldehyde derivatives (5b - f) were successfully derived to the alcohols (7b - f), which then reacted with MsCl/TEA, respectively. It is interesting to note that the yields of the oxazinones changed considerably depending on the substituents on the benzene ring, and results are summarized in the Table. Substitution of hydrogen by the electron-releasing substituents resulted in the formation of only oxazinones (8b - d) in high yields, while the presence of the chloro or nitro groups being electron- withdrawing substituents had a tendency to produce much amount of mesylates (9a, 9e, and 9f). The cyclization process seemed to be stereospecific giving a single oxazinone, respectively. The reported vicinal coupling constants ($^3J_{H-H}$) of 2-oxotetrahydro-1,3-oxazines are 3 - 5 Hz for the eq - eq protons and 9 - 10 Hz for the ax - ax protons in their ^1H nmr study.[4a,5] For instance, the ^1H nmr spectrum of 8c displayed a doublet (J=9.0 Hz) at 5.36 ppm corresponding to the C_6-proton and a doublet of doublets (J=10.0 and 6.0 Hz) at 3.14 ppm corresponding to the C_5-proton after irradiation at the C_6-proton. These values of the coupling constants are compatible with a proposed trans-stereochemistry of 8c having 5,6-di-equatorial configurations. Similar ^1H nmr data were obtained from the other oxazinones.



5a - f 7a - f 8a - f 9a, 9e - f

	R	Yield (%) of Oxazine	Yield (%) of Mesylate
a	H	36	47
b	CH_3	74	0
c	4-CH_3O	82	0
d	3,4-OCH_2O	83	0
e	4-Cl	34	53
f	4-NO_2	19	60

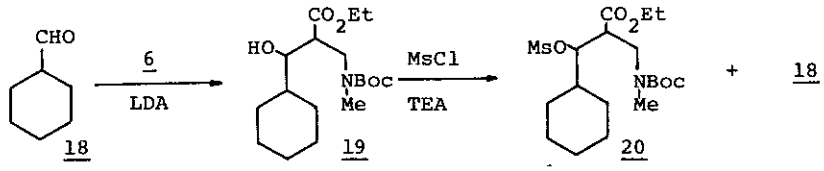
Next, the behaviors of the allylic alcohols (11 and 15), prepared from trans-cinnamaldehyde (10) and acrolein (14), were investigated. Unexpectedly, reaction of 11 with MsCl/TEA in CH_2Cl_2 afforded a mixture of two oxazinones (12 and 13) in a ratio of 4 : 1 in 60% combined yield, which were separated by column chromatography, together with unstable mesylate which was just detected on tlc. Based on the values of the coupling constants of their ^1H nmr spectra, the major isomer (12) [$J_{6(H)-5(H)}$=7.5 Hz, $J_{5(H)-4(ax-H)}$=9.0 Hz, and $J_{5(H)-4(eq-H)}$=6.0 Hz] was assigned as the trans-isomer having 5,6-di-equatorial configurations and the minor one (13) [$J_{6(H)-5(H)}$=4.0 Hz, $J_{5(H)-4(ax-H)}$=10.0 Hz, and $J_{5(H)-4(eq-H)}$=5.5 Hz] was assigned as the cis-isomer having an axial orientation of C_6-styryl group.



10 11 12 13

14 15 16 17

Analogously, reaction of 15 with MsCl/TEA gave the oxazinone (16) in 35% yield, accompanied by the mesylate (17) in 31% yield. Finally, reaction of the saturated alcohol (19), prepared from cyclohexylaldehyde (18), with MsCl/TEA was



carried out under similar reaction conditions, but contrary to our expectation no oxazinone was obtained at all and only the mesylate (20) was isolated in 64% yield with the recovery (22%) of the starting material. Although the mechanistic considerations of our reaction are now investigation, we provided a new and facile synthetic method of 6-aryl- or vinyl-substituted 2-oxotetrahydro-1,3-oxazines. Recently halonium-initiated cyclization of allylic-[6] or homoallylic-urethanes[7] to give the cyclic urethanes have been reported.

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3. 3: ir (liquid film) 1720 and 1700 cm^{-1}. ^1H nmr ($CDCl_3$) (selected data of oxazinone ring protons) 3.05 (3H, s, NCH_3), 3.27 (1H, ddd, J=6, 6, 5.5 Hz, 5-H), 3.39 (1H, dd, J=11, 5.5 Hz, 4-H_{ax}), 3.68 (1H, dd, J=11, 6 Hz, 4-H_{eq}), 5.65 ppm (1H, br d, J=6 Hz, 6-H). MS (m/z) 329 (M^+).
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