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# A MILD PROCEDURE FOR ETHERIFICATION OF ALCOHOLS WITH PRIMARY ALKYL HALIDES IN THE PRESENCE OF SILVER TRIFLATE

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**Abstract:** Alcohols were alkylated in good to excellent yield with primary alkyl halides by a method employing silver triflate and a non-nucleophilic amine base.

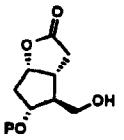
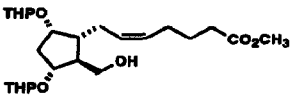
Alkylation of a hydroxyl group is a common practice in organic chemistry.[1] Since hydroxyl groups are present in numerous compounds of synthetic and biological interest, it is important to have suitable methods for effecting their protection and derivatization without disrupting the parent molecule.[2] Recently we found natural prostaglandins[3] (PGs) and synthetic PG intermediates to be extremely labile in alkoxide mediated alkylation techniques, thus requiring development of an alternative milder alkylation method. Silver triflate has been used extensively in conventional glycoside chemistry to mediate formation of 1,2-cis and 1,2-trans glycosidic bonds[4] *via* reaction of a glycosyl halide with an appropriate alcohol. However, we found these reaction conditions unsuccessful with non-activated alkyl halides.[5] We now wish to report a modified procedure that allows for reaction of an alcohol with an alkyl iodide in the presence of silver triflate and 2,6-di-*tert*-butylpyridine to provide ethers in good to excellent yields.

Results of our new procedure are summarized in Table 1. Primary, secondary and even tertiary alcohols underwent alkylation with primary alkyl iodides generally in good to excellent yields depending on the method employed. Prostaglandin $F_{2\alpha}$ methyl ester (entry 3) underwent alkylation with iodomethane to provide its 11-methyl ether as the sole product in 39% yield. Interestingly, the *bis*-THP protected alcohol (entry 6) could be alkylated with lesser reactive alkyl iodides such as 1-iodohexane and 1-iodooctane to yield the corresponding hexyl and octyl ethers in 62% and 64% yields, respectively. Finally, as demonstrated in entry 5 our method was also effective with allyl chloride, benzyl bromide, and even a 2° alkyl iodide (although in lower yield).

The following procedure is representative of this method: A solution of the alcohol (1.0 mmol), 2,6-di-*tert*-butylpyridine (1.5 mmol) and AgOTf (1.1 mmol) in $CH_2Cl_2$ (2.0 mL) was cooled to 0 °C. The alkyl halide (1.2 mmol) was added and a yellow precipitate formed within 15 min. After 1 h the reaction was diluted with $CH_2Cl_2$ and filtered through a plug of celite. The filtrate was washed with 1 N HCl, saturated aqueous $NaHCO_3$, brine, dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Products were isolated by flash column chromatography on silica gel.

In conclusion, we have provided a new procedure for etherification of alcohols with a variety of alkyl halides. Due to the mildness of this method we anticipate its future applications especially with sensitive natural products and synthetic intermediates.

**Table 1. Silver Triflate Assisted Etherification Of Alcohols.**

| Compound | RX | Method[a] | % Yield of ether[b] |
|---|---|---|---|
| 1. Geraniol | $CH_3I$ | A,B | 63,95 |
| | *n*-PrI | A,B | 60,96 |
| 2. Cholesterol | $CH_3I$ | A | 51 |
| | *n*-PrI | A | 45 |
| 3. $PGF_{2\alpha}$ methyl ester | $CH_3I$ | A | 39[c] |
| 4. 2-Phenyl-2-propanol | $CH_3I$ | A | 41 |
| 5.  P = p-phenylbenzoyl | $CH_3I$ | A | 73 |
| | $CH_3CH_2I$ | A | 49 |
| | *n*-PrI | A,B | 39,52 |
| | *sec*-PrI | A | 25 |
| | $PhCH_2Cl$ | A | 60 |
| | $CH_2$=$CHCH_2Br$ | A | 62 |
| 6.  | $CH_3(CH_2)_5I$ | B | 64 |
| | $CH_3(CH_2)_7I$ | B | 62 |

[a]Method A: Alcohol/AgOTf/R'X/2,6-di-*tert*-butylpyridine (1.0/1.1/1.2/1.5 ratio of equivalents)
Method B: Alcohol/AgOTf/R'X/2,6-di-*tert*-butylpyridine (1.0/3.0/3.2/3.5 ratio of equivalents)
[b]Isolated yield of pure products after silica gel chromatography. All products gave satisfactory $^1H$ NMR and mass spectral data
[c]11-Methoxy $PGF_{2\alpha}$6 was isolated as the sole product (98% yield based on recovered starting material)

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**References and Notes:**

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