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# The reaction of aryl triflates and aryl pivalates with electrophiles. The triflate as a *meta*-directing group

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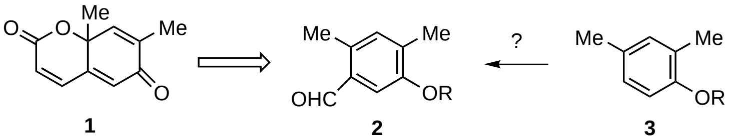
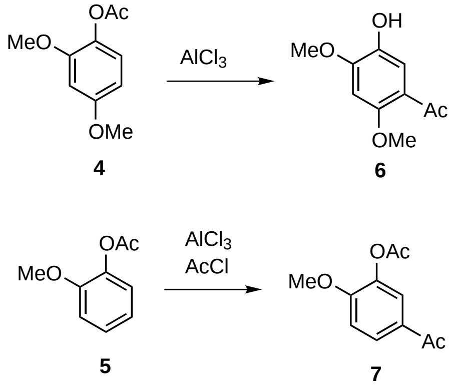
**Abstract**—Electrophilic reactions of substituted aryl triflates yield products wherein the substituents direct the regioselectivity of electrophilic substitution.

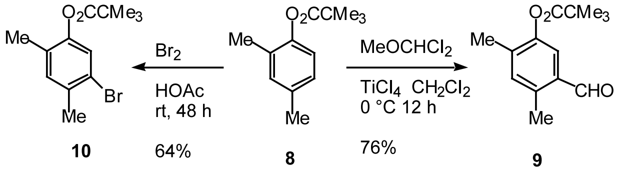


In the course of a synthesis of eurycolactone A, we required a direct route to lactone **1**.[1] After evaluating several possibilities; aldehyde **2** emerged as a direct precursor. Although phenol **3** (R = H) is inexpensive and readily available, electrophilic acylation would be expected to provide the *ortho*-hydroxy aldehyde rather than the *meta*-hydroxy aldehyde **2**. In this paper we protect the phenol with groups that convert the phenol into a net electron-withdrawing group and study the reactions of these compounds with electrophiles.

Ballio reported that the aluminum chloride-mediated intramolecular Fries transposition of aryl acetate **4** provided **6**.[2] Martin reported that the intermolecular acylation of **5** with acid chlorides afforded **7**.[3] Although products **6** and **7** were generated in 42 and 50% yields, respectively, minor products resulting from *ortho*-substitution were also obtained. To the best of our knowledge, no one has examined the generality of this strategy for electrophilic substitution.



We reasoned that a pivalate ester such as **8** would be more stable than the acetate. Thus, we synthesized pivalate **8** from the corresponding phenol using pivaloyl chloride and pyridine. The results of formylation and bromination of pivalate **8** are shown below. During the formylation reaction, small amounts (5–10%) of side products derived from cleavage of the pivalate ester were isolated. The formylation and bromination of the pivalate of 2-bromo-4-methylphenol afforded low yields of the desired products.



Attempted Friedel–Crafts alkylation led to decomposition of pivalate **8**. The structures of aldehyde **9** and bromide **10** were determined by proton NMR, $^{13}$C NMR, IR, and high resolution mass spectrometry. In the 2D NOESY NMR of **9**, an NOE interaction

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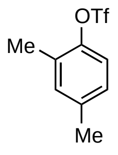
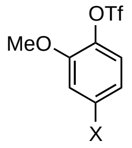
between the aldehyde and the methyl group at C-4 confirmed the regiochemical assignment. The regiochemistry of **10** was determined by 2D NOESY NMR (only one aromatic ring proton exhibited an interaction with the methyl group at C-4).

The triflate, a more durable electron-withdrawing group than the pivalate, was next studied. Triflates **11**–**14** were synthesized in excellent yields by treatment of the phenol with triflic anhydride and pyridine.[4] The reaction of triflates **11**–**14** with electrophiles afforded fewer byproducts. The triflates were compatible with a wider range of electrophiles. Triflates **11**–**14** afforded good yields of products in bromination, acylation and electrophilic alkylation reactions.[5] These results are collected in Table 1. The regiochemistry of the aldehydes was determined by 2D NOESY NMR experiments. The regiochemistry of the products from the reactions with the triflate of guaiacol was determined by examining the NMR splitting pattern of the aromatic ring protons. Each product exhibited $^1$H, $^{13}$C NMR, IR, a mass spectrum, and a high resolution mass spectrum in accord with the assigned structure. Interestingly, alkylation of triflates **12** and **13** with 2-bromopropane and aluminum chloride produced both the expected alkylation products and the products derived from alkylation followed by demethylation of the aryl methyl ether.

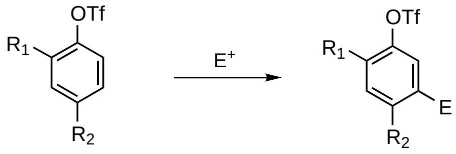


**11**



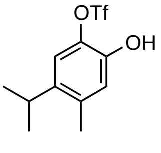
**12**: X = Me
**13**: X = Br
**14**: X = H

**Table 1.** Reaction of triflates with electrophiles

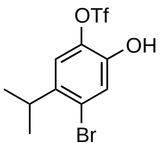


| $R_1$ | $R_2$ | $E^+$ | % Yield |
|---|---|---|---|
| Me | Me | $MeOCHCl_2/TiCl_4$, $CH_2Cl_2$, 0°C–rt, 12 h | 41 |
| OMe | Me | $MeOCHCl_2/TiCl_4$, $CH_2Cl_2$, 0°C–rt, 12 h | 96 |
| OMe | Me | $Br_2$/HOAc, rt, 12 h | 100 |
| OMe | Me | $CH_3COCl/AlCl_3$, $ClCH_2CH_2Cl$, rt, 6 h | 95 |
| OMe | Me | *i*PrBr/$AlCl_3$, $ClCH_2CH_2Cl$, rt, 30 h | 51[a] |
| OMe | Br | $MeOCHCl_2/TiCl_4$, $CH_2Cl_2$, 0°C–rt, 18 h | 47 |
| OMe | Br | *i*PrBr/$AlCl_3$, $ClCH_2CH_2Cl$, rt, 12 h | 42[b] |
| OMe | H | $MeOCHCl_2/TiCl_4$, $CH_2Cl_2$, 0°C–rt, 5 h | 99 |
| OMe | H | $CH_3COCl/AlCl_3$, $ClCH_2CH_2Cl$, 0°C, 12 h | 94 |

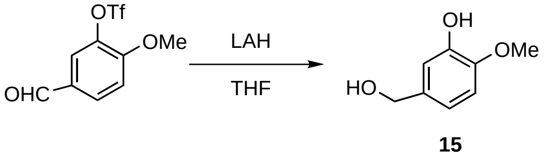
a: 34%



b: 56%



The results from Table 1 indicate that the triflate is stable under several reaction conditions. The triflate group is readily removed by treatment with lithium aluminum hydride.[6,7] As shown below, treatment with lithium aluminum hydride produces the known alcohol **15** in 100% yield.



**15**

The use of aryl triflates to control the regiochemistry of intermolecular acylation, bromination or alkylation should have broad application. The ease of triflate introduction coupled with the well-established organometallic chemistry of aryl triflates[8] combine to offer many avenues for elaboration.

## Acknowledgements

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5. To a solution of 2-methoxy-4-methyl phenyl triflate (0.247 g, 0.915 mmol) and dichloromethyl methyl ether (0.124 mL, 1.37 mmol) in methylene chloride (2 mL), was added dropwise $TiCl_4$ (0.281 mL, 2.56 mmol) at 0°C under Ar. The resulting mixture was stirred overnight to rt. The reaction was poured into ice water and extracted with methylene chloride. The organic layer was washed with $NaHCO_3$ and brine and then dried with $MgSO_4$ and evaporated in vacuo. The crude material was purified by silica gel flash chromatography using 5:1 hexanes:ethyl acetate.
   4-Methoxy-2-methyl-5-trifluoromethanesulfonyloxybenzaldehyde: $^1$H NMR ($CDCl_3$) 2.72 (s, 3H), 4.01 (s, 3H), 6.89 (s, 1H), 7.69 (s, 1H), 10.15 (s, 1H). $^{13}$C NMR ($CDCl_3$) 19.3, 56.7, 115.8, 118.8 (q, $J=318$ Hz), 124.8, 127.5, 137.2, 143.7, 155.4, 189.4. IR (film) 2870, 1709, 1607. MS $m/z$ 300, 298, 165, 109. HRMS $m/z$ for $C_{10}H_9F_3O_5S$: calcd 298.0123, found: 298.0127.
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