Tetrahedron Letters, Vol. 33, No. 15, pp. 1959-1962, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

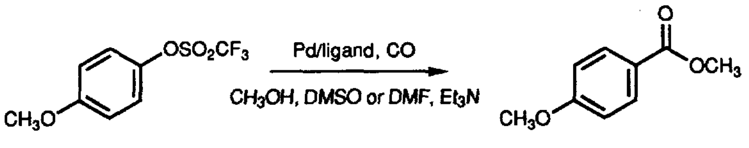
Alkoxycarbonylation Reactions Using Aryl Fluorosulfonates

Gregory P. Roth* and Jeanine A. Thomas

Bristol-Myers Squibb Pharmaceutical Research Institute
5 Research Parkway
Wallingford, Connecticut 06492

Summary: Aryl fluorosulfonates are shown to undergo palladium catalysed alkoxycarbonylation with a variety of alcohols under mild basic conditions at ambient CO pressure.

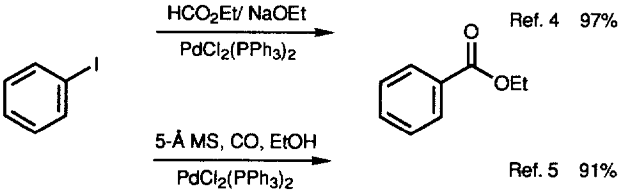
There are several accounts in the literature describing the transition metal catalyzed carbonylation of aryl halides and aryl triflates in the presence of an alcohol or amine to provide the corresponding ester or amide product. This direct introduction of a carbonyl group into a molecule can be accomplished by a variety of methods. Cacchi, Ortar, and coworkers[1] have reported that a variety of enol and aryl triflates readily undergo oxidative addition to palladium followed by migratory insertion of CO with subsequent attack by nucleophilic alkoxide to furnish the desired ester. This methodology was further elaborated and optimized by Dolle and coworkers[2] with their demonstration that use of the dppp ligand (1,3-bis(diphenylphosphino)propane) instead of triphenylphosphine or dppf (1,1'-bis(diphenylphosphino)ferrocene) in a Pd^{II} complex afforded *ca.* 500-fold rate enhancement and subsequently higher yields.



Ligand = dppf (ref. 1) 59%
dppp (ref. 2) 84%

Eq. 1

Aryl bromides and iodides will also undergo similar transformation, albeit under more forcing conditions.[3,4] Treatment of the desired substrate with a sodium alkoxide and alkyl formate as a source of CO in the presence of a palladium catalyst complex, under high pressure in a heated sealed tube, furnishes the desired ester in high yield. More recently, these substrates have been shown to undergo alkoxycarbonylation under base free conditions[5] as illustrated in Equation 2. In this procedure the reaction is conducted in the presence of molecular sieves and a palladium or cobalt catalyst, the only drawback being the need for a high pressure (30 atm) CO atmosphere.

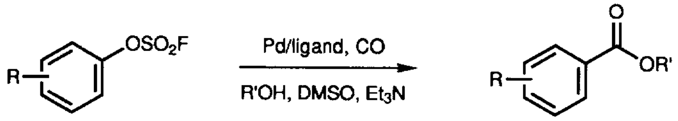


Eq. 2

We recently described new utility for a leaving group that previously had not received much attention by the synthetic community. Aryl fluorosulfonates[6] as well as the enol fluorosulfonate derived from a cephalosporin nucleus[7] were shown to be easy to prepare from the parent enol or phenol using diisopropylethylamine and fluorosulfonic anhydride at -78°C. These novel substrates behaved in a manner consistent and identical to that of the corresponding triflate in palladium mediated coupling reactions with organostannanes and organozinc halides.

In order to further define the scope and limitations in using the fluorosulfonyloxy moiety as a triflate alternative we have explored its utility and effectiveness as a coupling partner in carbon monoxide insertion reactions such as alkoxycarbonylation. We are pleased to report that aryl fluorosulfonates behaved as expected and underwent alkoxycarbonylation in good to excellent yields. Table 1 summarizes the results of this investigation.

Table 1. Palladium-Catalysed Alkoxycarbonylation of Arylfluorosulfonates



Entry	R	Method[a]	R'OH	% Yield[b]
1	H	A	MeOH	48
2	H	B	MeOH	88
3	H	B	i-PrOH	80
4	H	B	n-BuOH	72
5	4-OMe	B	MeOH	58
6	4-NO_2	B	MeOH	44
7	4-$COCH_3$	B	MeOH	83
8	3-CO_2CH_3	B	MeOH	92
9	2-Naphthyl	B	MeOH	85

a. Method A: procedure as described in ref. 1, Method B: procedure as described in this communication; b. isolated yield of pure product.

In a typical procedure (entry 2), a deoxygenated solution of phenylfluorosulfonate (1.0 equiv.), dppp ligand (0.03 equiv.), and triethylamine (1.1 equiv.) in DMSO/methanol (3:2; *ca.* 4 mL on a 1 Mmole scale reaction) is treated with $Pd(OAc)_2$ (0.03 equiv.) and is then saturated with CO by bubbling a stream of gas into the reaction mixture for 15 min at ambient temperature. The mixture is then allowed to stir at 60°C under a CO atmosphere for 2 hours. Workup consisted of partitioning the reaction mixture between water and ethyl acetate and washing the organic fraction with additional aliquots of water then brine. After drying ($MgSO_4$) and concentration, the crude products were purified by column chromatography.

When dppf was used as a ligand (entry 1) conversion to the desired product was sluggish. The yield was lower, due to a short catalyst lifetime, which resulted in precipitation of palladium black. This occured in experiments where the catalyst complex formed *in situ via* ligand exchange or when a $Pd(Cl)_2$dppf complex[8] was prepared and then utilized. The results in the Table illustrate that a variety of functional groups are tolerated under the basic reaction conditions. Although there is evidence that electron withdrawing substituents enhance reaction rate for some examples of transition metal mediated aryl couplings,[9] we noticed a competing side reaction in entry 6. The balance of reaction product was predominantly the corresponding p-nitrophenol resulting from sulfur-oxygen bond cleavage, as well as some decomposition product. Entry 9 represents the conversion of 2-fluorosulfonylnaphthalene to the corresponding methyl ester. In comparison, the analogous triflate has been reported to furnish the desired ester in 78% yield.[1] With respect to the alcohol component of the reaction, yields seemed to decrease as larger alcohols were used and tert-butanol did not prove to be synthetically useful.

In conclusion, we have demonstrated the utility of the fluorosulfonate leaving group as an inexpensive alternative for triflate in alkoxycarbonylation reactions mediated by palladium. At present, we are investigating homologation reactions of aryl and enol fluorosulfonates and have had preliminary success with aryl ketone formation as well as ketone and ester formation of several enol fluorosulfonates.

Acknowledgements: The authors wish to thank the Analytical Research department at Bristol-Myers Squibb for all analytical determinations required for this project.

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(Received in USA 23 December 1991)