Pergamon

Tetrahedron Letters 42 (2001) 265–266

TETRAHEDRON LETTERS

Practical synthesis of acetophenones from phenoltriflates

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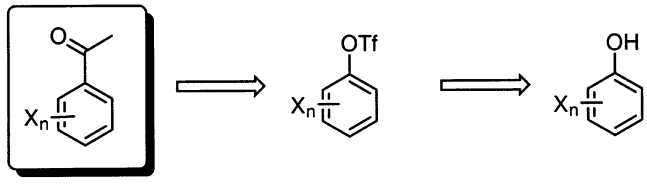
Received 29 September 2000; accepted 23 October 2000

Abstract—A new practical method for the preparation of acetophenone from aryl triflates is reported. The acyl group is installed by a mixture of $SnMe_4$, Pd(0) and CO (balloon), using a three-component procedure.

Acetophenones are valuable derivatives, especially useful for the synthesis of heterocycles for medicinal chemistry purposes.[1] Their preparations, based on a direct Friedel–Crafts acylation[2] of substituted arenes, usually gave isomeric mixtures of products which require tedious purification by non-conventional methods.[3] In the course of the multi-step synthesis of bioactive compounds we needed isomerically pure acetophenones as starting materials. These compounds were either not commercially available or were sold as mixtures of regioisomers. In a literature survey, we found that acetophenones were prepared in a two-step sequence from the corresponding phenols via the phenoltriflates as shown below (Scheme 1).

When we first tested either the conditions already described by Cabri and co-workers,[4] fevering a Heck reaction of a phenol triflate in presence of butyl vinyl ether followed by an acidic work-up, or those reported by Stille and co-workers[5] recommending a palladium-catalyzed carbonylative coupling in the presence of $SnMe_4$, we were disappointed to get a low yielding transformation. However, after some experimentation where the methodologies of both protocols were combined in a three-component procedure associated with $Pd(OAc)_2$, we were pleased to observe the formation of the acetyl compounds in very high yields. Several points are worth noting: (i) $Pd(OAc)_2$ is an appropriate precatalyst; (ii) in contrast to Stille's report, dppp is very efficient as a ligand for Pd(0) when performing the acylation;[5b] (iii) LiCl is not required;[5b] (iv) saturation of the reaction mixture with CO is decisive, unless the corresponding methylation occurred as a side reaction.[5c] Finally, the procedure reported in this letter represents an improved and practical synthesis of acetophenones or equivalent **1**–**6** (isomer-free) from phenoltriflates[6] in very good yields (70–94%) (Scheme 2).

Typical experimental procedure:
In a 250 ml flask equipped with a condenser, a mixture of 4-chloro-3-methylphenoltriflate (9.29 g, 33.8 mol, 1.0 equiv.) and Et_3N (11.72 ml, 84.5 mmol, 2.5 equiv.) in dry DMF (60 ml) was stirred at rt, while a flux of argon was gently bubbled into the mixture for 30 min. Then, the inert atmosphere was replaced by a flux of CO (kept for the whole reaction). After 15 min, $SnMe_4$ (9.37 ml, 67.6 mmol, 2.0 equiv.) was added into the mixture. After further 15 min, $Pd(OAc)_2$ (228 mg, 1.0 mmol, 3 mol%) and dppp (558 mg, 1.3 mmol, 4 mol%) were added and the reaction mixture was heated to 60°C for 2 h. Then, the CO atmosphere was replaced by a flux of argon and the temperature was allowed to cool to rt. The reaction mixture was poured into satd NH_4Cl and diluted with diethyl ether. The organic layer was succes-



Scheme 1. Synthesis of acetophenone derivatives from phenols via phenoltriflates.

Keywords: palladium catalysis; carbonylation; acylation.

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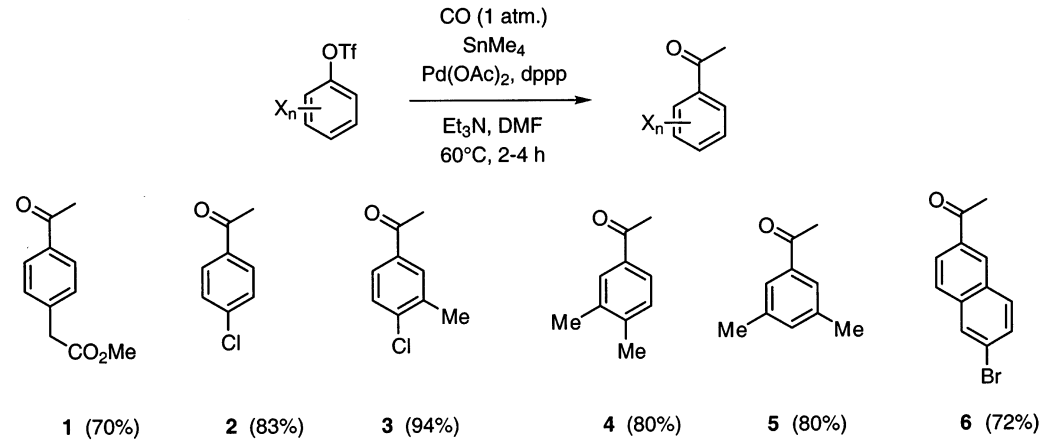
0040-4039/01/$ - see front matter
PII: S0040-4039(00)01935-3



Scheme 2. Acetophenones prepared using the three-component reaction.[8]

sively washed with water and brine, dried (Na_2SO_4) and decolorized over charcoal, filtered through Celite and concentrated. The crude was purified by chromatography on silica gel (Et_2O/hexanes: 20/80) to afford pure 4-chloro-3-methylacetophenone **3** (5.40 g, 32.0 mmol) in 94% yield as a pale yellow oil.[7]

Acknowledgements

F. Garrido was funded by Bioprojet (Paris) and this work was supported in part by the University of Toronto (Canada).

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7. Allen, C. F. H.; Bridges, M. P. *J. Am. Chem. Soc.* **1927**, *49*, 1826. Compound **3** can be distilled (bp 104°C, 0.4 mmHg).
8. All compounds have been fully characterized by ^1H and ^{13}C NMR, IR, MS and HRMS.