ORGANIC LETTERS

2007
Vol. 9, No. 4
667−669

One-Step Synthesis of α-Chloro Acetophenones from Acid Chlorides and Aryl Precursors

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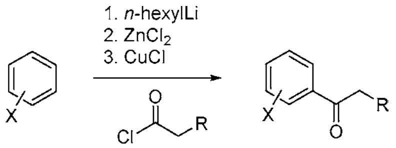
Received December 7, 2006

ABSTRACT



R = H, Cl, OBn, 4-ClPhO

A direct and efficient method was developed for the preparation of a variety of substituted acetophenone derivatives from readily available arene precursors and acid chlorides. This method has significant generality and affords access to substitution patterns on aryl rings not directly achievable by Friedel–Crafts chemistry.

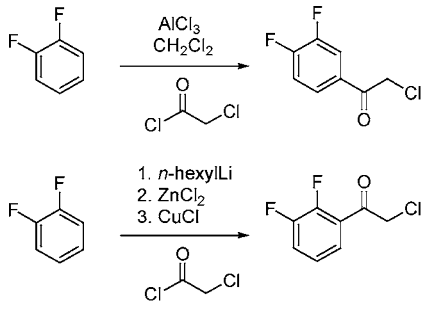
Fluorinated aromatics are critical starting materials for the preparation of pharmaceutically active and marketed compounds due to a number of reasons: (1) many modern drugs contain fluorinated aromatics; (2) simple fluorinated aromatics are readily available; and (3) chemistry to strategically place a fluorine on an arene ring has not been fully developed. As a consequence, methods that can elaborate simple fluorinated aromatics to more useful intermediates would find wide use in the pharmaceutical arena. Particularly attractive compounds are α-chloro acetophenones; these are excellent substrates for asymmetric reductions, and the acetophenone carbonyl also serves as a suitable electrophile for various nucleophilic addition reactions.

We recently required access to 2-chloro-1-(2,3-difluorophenyl)-ethanone (**2b**) directly from 1,2-difluorobenzene. Traditional Friedel−Crafts chemistry was unsuitable for our purposes due to very selective acylation in the undesired meta position (Scheme 1).[1]

Investigation of the literature revealed little precedent for such a transformation. The Pd-catalyzed coupling of an α-chloro thiol ester with an aryl boronic acid has been reported; however, this route was unattractive due to the necessity of preparing the thiol ester, the added expense of the boronic acid, and the use of a stoichiometric copper reagent.[2] Other examples, such as the addition of nucleophiles to Weinreb amides,[3] palladium-catalyzed acylations of arylboronic acids[4] and arylzinc compounds,[5] iron-catalyzed cross-couplings of acyl chlorides and Grignard reagents,[6] acylation of arylcuprates,[7] and cobalt-,[8] rhodium-,[9] and vanadium-catalyzed coupling reactions,[10] all suffered from similar shortcomings.

By analogy to the copper-catalyzed addition of alkylzinc halides to acid chlorides, we reasoned that an ArZnX species

Scheme 1



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[1] Bercher, H.; Ehlers, D.; Grisk, A. *Pharmazie* **1976**, *31*, 351−354.

10.1021/ol0629667 CCC: $37.00

should add to chloroacetyl chloride in a copper-catalyzed reaction.[7] Herein, we report the direct synthesis of a variety of substituted acetophenones in one step from the corresponding aryl precursor.

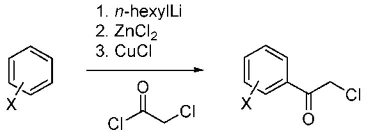
It was found that ortholithiation of 1,2-difluorobenzene was possible using *n*-hexyllithium at −65 °C; however, rapid decomposition was observed at temperatures above −50 °C.[11] Direct acylation of the aryllithium species at −65 °C did not yield any significant amount of product, and reverse addition was unfeasible due to warming during transfer.

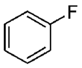
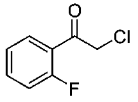
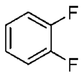
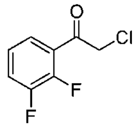
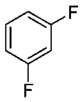
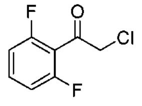
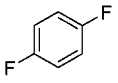
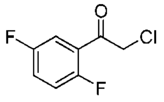
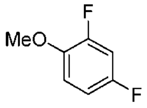
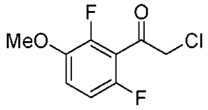
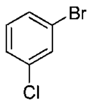
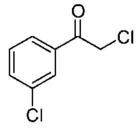
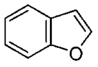
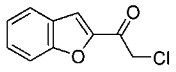
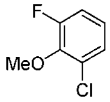
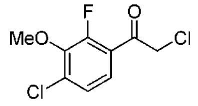
Transmetalation using zinc chloride did proceed cleanly at −65 °C, and the corresponding aryl zinc species was found to be stable even at room temperature. When treated directly with chloroacetyl chloride, no reaction was observed due to the weak nucleophilic character of the aryl zinc moiety, and upon warming, extensive decomposition occurred with minimal product formation. Catalytic cuprous(I) cyanide (10 mol %) was added in hopes of activating the acyl chloride, and indeed, this successfully effected clean acylation. Further optimization revealed the same loading of CuCl as a suitable substitute for CuCN.[12]

This general procedure was applied to a variety of substrates (Table 1). Typical assay yields were ~70%, and most of the products could be isolated by crystallization from heptane at −30 °C without chromatography.[13]

It is interesting to note the positional contrast of several of these products relative to their Friedel−Crafts product. In the case of **1a**, the 4-fluoro acetophenone is the product of Friedel−Crafts acylation,[14] as opposed to the 2-fluoro isomer **2a**. Similarly, as previously noted, **1b** yields the 3,4-difluoro acetophenone instead of the desired 2,3-difluoro isomer. The acylation of **1c** using aluminum chloride has been shown to form the 2,4-difluoro isomer.[15] Attempts at forming 2,6-difluoro acetophenones such as **2c** have all involved multistep sequences,[16] whereas our method can accomplish this in one step.

Table 1. Acylation with Chloroacetyl Chloride



entry	aryl	product	yield[a]
1	 **1a**	 **2a**	78[b]
2	 **1b**	 **2b**	79
3	 **1c**	 **2c**	54
4	 **1d**	 **2d**	78
5	 **1e**	 **2e**	73
6	 **1f**	 **2f**	65
7	 **1g**	 **2g**	68
8	 **1h**	 **2h**	75

[a] HPLC assay yield based on comparison to purified reference standard.
[b] *sec*-Butyllithium substituted for *n*-hexyllithium.

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(11) Thermal stability of 2,5-difluorophenyl lithium: Scott, J. P.; Brewer, S. E.; Davies, A. J.; Brands, K. M. J. *Synlett* **2004**, 1646−1648.

(12) Control experiments indicate that stoichiometric CuI can be substituted for $ZnCl_2$ and 10 mol % of CuCl. For ease of processing, workup, waste disposal, and reaction robustness, especially on a large scale, we have developed this methodology using stoichiometric zinc and catalytic copper. Further experiments will be required to determine if the CuCl is activating the acid chloride or if transmetalation from zinc to copper is in fact taking place. Substituting catalytic CuI for $ZnCl_2$ yields almost no product by HPLC.

(13) The use of commercially available PhZnBr as well as transmetalation with $PhMgCl/ZnCl_2$ gave the product in 40−45% assay yield.

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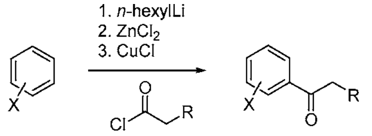
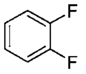
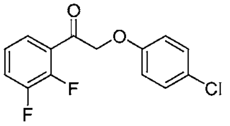
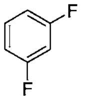
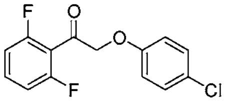
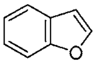
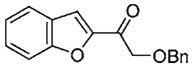
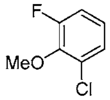
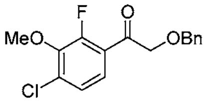
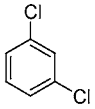
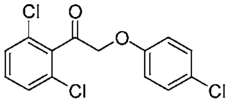
Table 2. Acylation with 4-Chlorophenoxyacetyl Chloride and Benzyloxyacetyl Chloride



R = OBn or 4-ClPhO

entry	aryl	product	yield[a]
1	 **1b**	 **3b**	83
2	 **1c**	 **3c**	72
3	 **1g**	 **3g**	60
4	 **1h**	 **3h**	70
5	 **1i**	 **3i**	65

[a] Isolated yield.

Trisubstituted **1h** illustrates not only different positional control achieved by using this method but also an advantage regarding reactivity. Under typical Friedel–Crafts conditions, acylation occurs exclusively para to the methoxy group; however, the deactivating nature of the halogens retards the reaction to such an extent that deprotection of the anisole proceeds at a competitive rate. Consequently, extensive *O*-acylation is also observed in addition to the formation of the expected acetophenone. In contrast, deprotonation occurs ortho to the fluorine in this substrate ultimately yielding **2h**, with no deleterious effect on the anisole methyl group. Although not demonstrated, it is reasonable to expect similar issues were one to attempt a Friedel–Crafts acylation using 2,4-difluoroanisole (**1e**).

Benzofuran (**1g**) is known to be an unsuitable substrate for Friedel–Crafts acylations[17] due to polymerization initiated by strong Lewis acids. Deprotonation at the 2 position is readily accomplished with *n*-hexyllithium, and the resultant aryllithium species is stable at temperatures below −60 °C. Following our procedure, acylation was achieved in 68% yield.

In an effort to increase the scope of this chemistry, we examined the effects of generating the aryllithium species via halogen metal exchange as opposed to deprotonation. When 3-chloro bromobenzene (**1f**) was subjected to our procedure, we were pleased to observe that **2f** was obtained in a reasonable 65% yield. This result allows for the possibility of controlling the positional outcome of acylation reactions using highly substituted substrates based on the position of bromine as opposed to the specific electronics of the aryl system. This methodology is not compatible with strong amine bases such as LDA.

The chloroacetophenone products produced in this study represent a class of compounds with high synthetic value. Asymmetric reduction of acetophenones via established methods such as DIP–Cl, OAB/borane, and asymmetric hydrogenation could be employed to supply the corresponding chiral benzylic alcohol.[18] Base-catalyzed ring closure would then allow access to a variety of chiral styrene oxides. In addition, the acetophenone carbonyl is a suitable electrophile for a wide spectrum of nucleophilic additions, affording access to highly substituted tertiary alcohols and epoxides which can be further elaborated.

Hoping to demonstrate compatibility with other acyl chlorides as well as to introduce additional functionality to the acetophenone products of this chemistry, we explored the use of a phenoxyacetyl chloride and a benzyloxyacetyl chloride. As can be seen in Table 2, this procedure yields results similar to those obtained using chloroacetyl chloride. The benzyloxy series of compounds similarly allows access to diol analogues, again with the potential for stereocontrol at the benzylic center.

To validate the compatibility of our procedure with acetyl chloride, 1,2-difluorobenzene (**1b**) was acylated to yield 2,3-difluoroacetophenone in 72% yield.

We have demonstrated an operationally simple method for the one-step acylation of substituted aryl systems. This method allows access to products which cannot be prepared by traditional Friedel–Crafts acylations. The tolerance of multiple substituents on the aryl ring, including ones that are typically deactivating or incompatible with strong Lewis acids, makes this an attractive addition to the synthetic methods of medicinal chemistry by allowing for the generation of analogues. Furthermore, additional functionality can be introduced as part of the acid chloride moiety, further expanding the options for synthetically useful intermediates.

Acknowledgment. We thank Robert Reamer and Lisa DiMichele of Process Research, Merck & Co., Inc., for assistance with NMR spectral analysis.

Supporting Information Available: Experimental procedures and compound characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0629667

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