One-pot transformation of esters to analytically pure ketones: methodology and application in process development

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**ABSTRACT**

A convenient, single-pot protocol for the transformation of esters into analytically pure ketones is described herein. This method circumvents the need for purification and affords near quantitative yields for all substrates investigated. As a test of its utility, the method is used to improve the yields of a process for preparing a pharmacologically relevant anti-HIV intermediate by nearly 10 fold.

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The design, discovery, and synthesis of biologically active compounds are fundamental components of medicinal chemistry research. Methodology research, on the other hand, focuses on developing the tools required to facilitate important synthetic transformations, as well as providing workarounds for known lengthy synthetic sequences. While we were developing a structure activity relationship for a new class of compounds that are potent dual-tropic anti-HIV entry inhibitors, we needed access to building block 4 (Scheme 1).1 Compound 4 is an important intermediate in a class of CCR5 antagonists that had been previously developed at Merck.2–4 Unfortunately, no experimental procedures were provided for its synthesis, thereby making it more challenging for us to follow up on the use of the series.

Our lab initially attempted to scale up compound 4 using the conditions alluded to in the original set of publications. We found that, in the absence of an explicit procedure, we were only able to prepare small amounts of the desired material over the course of six steps. To address this problem, it appeared that developing a one-pot route to intermediate 3 might be the quickest way of improving the efficiency of the synthesis. To achieve this, we focused our attention on the Weinreb amide synthesis and subsequent Grignard reaction used for the conversion of ester A to ketone 3.5,6 Specifically, when we used ‘standard’ conditions for forming the Weinreb amides (i.e., multiple equivalents of alkyl-aluminum chlorides), followed by addition/elimination with a Grignard reagent,7 we observed significant quantities of impurities that necessitated a separate purification step. As an alternative, we considered the use of Grignard/N,O-dimethylhydroxylamine combinations to form Weinreb amides, a strategy used in several publications.7,8

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In this regard there are numerous reports that generate Weinreb amides from esters using non-nucleophilic Grignard reagents, followed by subsequent addition of nucleophilic Grignard reagents to afford the corresponding ketone in a two-step fashion with isolation and purification in between. Surprisingly, however, we were unable to find any literature that discussed single pot ketone forming reactions that utilize Weinreb amide/Grignard reagent combinations. As a consequence, we decided to explore the scope and limitation of this approach.

Initial attempts at the one pot process provided surprisingly straightforward and robust results (Table 1). We initially chose to use 4.5 equiv of the relevant Grignard, 1.2 equiv of N,O-dimethylhydroxylamine hydrochloride, and an A–B–C addition paradigm. Varying the temperatures (entry 1–3) using these conditions on a half mmol scale produced excellent results, with no double addition side-products and yields over 95% of pure material after a simple work up. Since chemical intuition might suggest that room temperature additions might have selectivity issues, all nine permutations were tested in duplicate. Although cooling was not required on this scale, the exotherm that was produced led us to select 0°C for all further attempts. Variation in the number of equivalents of Grignard reagent had virtually no effect on the observed product ratios (entry 4–6). When we used 3.5 equiv with careful drying and handling of reagents, the yields were consistently over 95% yield and the products that were isolated by simple extractions exhibited excellent purity. Reactions performed with 4.5 equiv were much less sensitive to small amounts of water (i.e., non-distilled THF could be used). Indeed, even when 10 equiv of Grignard (i.e., non-distilled THF could be used). Indeed, even when 10 equiv were much less sensitive to small amounts of water (i.e., non-distilled THF could be used). Indeed, even when 10 equiv of Grignard reagent were used, we only observed trace amounts of double addition. As a consequence 4.5 equiv of Grignard reagent were used in all subsequent experiments. Next, we probed the order of addition (entries 7–9). As expected, adding either the ester or N,O-dimethylhydroxylamine hydrochloride first did not affect the outcome of the reactions. Similarly, addition of the Grignard reagent in excess prior to the addition of the ester did not result in any over addition and pure material was still obtained after a simple extraction. From a mechanistic perspective these results suggest that both tetrahedral intermediates (i.e., the orthoamide bonding intermediate formed from the addition of hydroxylamine and the ketal intermediate formed by addition of the Grignard reagent) must be exceedingly stable at 0°C in THF. From a practical perspective it suggests that, if a given reaction failed to go to completion (due to wetness, bulkiness of substrate, or old Grignard reagent), one can simply add more Grignard to finish the reaction with no fear of byproducts. For simplicity, we decided to move forward with the more logical order of addition where the Grignard is added last.

To illustrate the reaction scope, we first varied the identity of the Grignard (Table 2). Being significantly more nucleophilic than phenethyl, we wondered if methylmagnesium bromide might result in over addition (entry 10). This was not the case, since the reaction product was once again produced in high yield and high purity after a simple extraction. By contrast, addition of methyl lithium under the same conditions produced a significantly poorer mono to di-addition ratio (entry 11), suggesting that magnesium-stabilized tetrahedral intermediates and more stable than their lithium counterparts. Continuing our exploration of aliphatic Grignard reagents, we next demonstrated that additions of primary alkyl Grignard reagents (entries 12) proceeded smoothly. By contrast, attempts to add secondary Grignard reagents, such as isopropylmagnesium chloride and cyclohexylmagnesium bromide, resulted only in the formation of the Weinreb amide with no detectable ketone being observed (entries 13 and 14).

We realized that the low reactivity of bulky Grignard reagents could, in selective cases, be used to our advantage. Having to use several equivalents of highly reactive Grignards could easily be avoided. For example, by first forming the Weinreb amide in situ using isopropylmagnesium chloride, we only needed to add ethynyl magnesium bromide in slight excess to produce the corresponding ethynyl ketone in high yield and purity (entry 15). This example is particularly noteworthy as the resulting ethynyl ketone is not stable to column chromatography and polymerizes upon concentration. Being able to use entry 15 as a pure solution in THF in subsequent reactions was highly advantageous compared to previous procedures.

With our reaction scope and limitations established, we returned to our original task of making compound 4 on a multi-gram scale (Scheme 2). Upon subjecting up to 25 g of ester 7 to our optimized conditions, quantitative yields of ketone 3 were obtained. This material was then subjected to the formylation/cyclization reaction. We initially attempted to combine the formylation and cyclization reagents shown in Scheme 1 and were disappointed to largely recover our starting material. Since quenching the reaction mixture generated ample amounts of hydrogen gas, we concluded that the first deprotonation event was failing (Scheme 3). Fortunately, addition of catalytic 15-crown-5 caused rapid evolution of hydrogen gas and allowed us to produce pyrazole 4 in good yield.
The reaction is quite robust and tolerates a large excess of ketones from esters using two classic reactions in a one-pot fashion. The reaction is tracked by LCMS. After an additional hour the reaction was partitioned between water and EtOAc three more times. The organic layers were combined, dried over anhydrous sodium sulfate, and filtered to afford 1-(1-benzylpiperidin-4-yl)-3-phenylpropan-1-one (3.302 g, 98% yield). Used for entries 1–14 and 16–17.

13. General procedure B: Methyl 1-benzylpiperidine-4-carboxylate (23 g, 1.0 mmol) as a solution in THF (20 mL, .05 M) was added to a flame dried 500 mL round bottom flask containing N,O-dimethylhydroxylamine hydrochloride (12.2 g, 1.2 mmol, 1.2 equiv) and stirred at 0 °C. Phenethylmagnesium chloride (2.3 mL, 4.5 mmol, 4.5 equiv) was then added followed by the reaction was allowed to stir until complete conversion to the ketone was observed by LCMS. The reaction mixture was quenched with a solution of saturated NH4Cl (5 mL) slowly and allowed to stir for 10 min, then basified with 10% NaOH dropwise. The mixture was further partitioned with EtOAc and separated. The aqueous layer was extracted with EtOAc once more and then DCm twice. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 1-benzyl-4-((4-benzyl-1H-pyrazol-3-y1)piperidine (2.1 g, 57% yield).

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Supplementary data
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References and notes
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In conclusion, we have developed a new method for the formation of ketones from esters using two classic reactions in a one-pot fashion. The reaction is quite robust and tolerates a large excess of exogenous nucleophile/base, a wide range of temperatures, and any order of addition. To demonstrate its utility, we showed that incorporating the one-pot reaction in a telescopic process toward biologically relevant pyrazole 4 resulted in a nearly tenfold increase in yield and decreased the number of synthetic operations from six to two.