Synthesis of Trifluoromethyl Ketones Using Polymer-Supported Reagents

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Abstract: A two step synthesis of trifluoromethyl ketones from aldehydes is reported. A combination of polymer-supported reagents and sequestering agents were employed to effect the transformation without the need for chromatographic purification.

INTRODUCTION

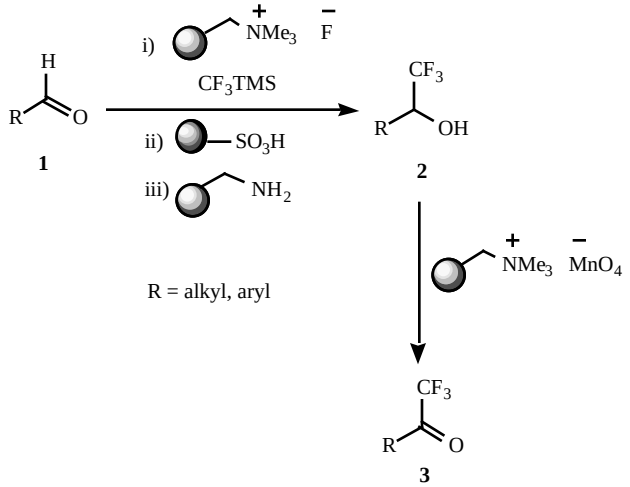
The past decade has seen the establishment of combinatorial chemistry in drug discovery programs as a convenient tool to generate a large array of diverse compounds for high throughput screening [1]. Although solid phase organic synthesis methods are now commonly employed, recent advances in solution phase synthesis are beginning to have significant impact. In particular, the application of solid-supported reagents are increasing in popularity [2,3]. These reagents offer tremendous advantages by combining the benefits of both solution and solid phase chemistry. Our group has contributed to this field of research through the development of a number of polymer-supported reagents[3] and their application in the *multi-step syntheses* of small libraries of heterocyclic molecules[4] as well as more complex natural products.[5] We now wish to report the use of a combination of polymer-supported reagents and sequestering agents to effect a clean preparation of trifluoromethyl ketones from aldehydes.

Fluorinated compounds have been extensively investigated by synthetic and medicinal chemists owing to their unique biological and physical properties[6]. For example, the incorporation of a trifluoromethyl ketone moiety into substrate analogues of hydrolytic enzymes has led to the development of several potent inhibitors of these enzyme systems [7].

A straightforward procedure for the preparation of trifluoromethyl ketones relies on the fluoride induced trifluoromethylation of aldehydes using trimethyl(trifluoro-methyl)silane (the Ruppert reagent) followed by subsequent oxidation of the trifluoromethyl substituted carbinols [8].

RESULTS AND DISSCUSSION

We have shown that a variety of aldehydes react smoothly with trimethyl(trifluoromethyl)silane in the presence of fluoride ions supported on Amberlyst A-27 resin (table 1 and scheme 1) [9].



Scheme 1. Transformation of aldehydes to trifluromethyl ketones using polymer-supported reagents

Reaction work-up involved quenching with Amberlyst A-15, an acidic ion-exchange resin, followed by sequestering any unreacted aldehyde starting material using aminomethylated polystyrene (AM-resin) [10]. The trifluoromethyl carbinols were obtained in good yields and purity after filtration and evaporation *in vacuo*. Trifluoromethyl carbinol products are known to be resistant to oxidation, but this may be achieved using the Dess-Martin periodinane oxidant, although some examples of Swern and basic aqueous potassium permanganate oxidations have also been reported [11].

In this work, various solid-supported oxidising agents were investigated with the best results being obtained using permanganate supported on Amberlyst A-27 [12,13]. The reactions were conducted in refluxing methylene chloride in the presence of 4Å molecular sieves to act as a dehydrating agent (THF or toluene can also be used if higher reaction temperatures are required). Under these conditions only aryl substituted alcohols reacted cleanly affording, after filtration over celite and careful evaporation *in vacuo*, the

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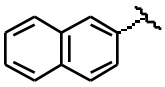
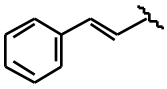
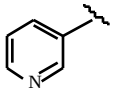
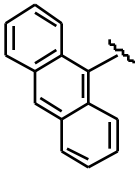
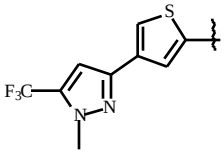
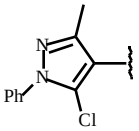
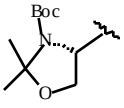
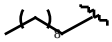
Table 1. Trifluoromethylation of Aldehydes and Oxidation of Trifluoromethyl Alcohols

Entry	R	Alcohol[a] (2) Yield%[b]	Purity%[c]	Ketone[a] (3) Yield%[b]	Purity%[c]
a	Ph	100	99	-[e]	-
b	*p*-NO_2Ph	75	99	-[f]	-
c	*p*-ClPh	97	95	100[g]	90
d	*p*-FPh	98	95	-[g,h]	95
e	*p*-OMePh	100	99	100	90
f		97	95	-	-
g		100	95	78	96
h		89[d]	99	-	-
i		67	98	100	96
j		85	99	75	95
k		79	100	74[i]	89
l		100	95	-	-
m		100	95	-[f]	-

Reagents and conditions: Trifluoromethylation of aldehydes: i) 1a-m, $TMSCF_3$(3 eq), A-27 (F^- form), THF, RT, 1-19 h; ii) A-15; iii) AM-resin; Oxidation of trifluoromethyl alcohols: 2, A-27 (MnO_4^- form), 4Å molecular sieves, CH_2Cl_2, reflux, 2-7 h. [a] All products were identified by ^1H, ^{13}C NMR and MS spectra. [b] Yields for reaction from precursor compounds. [c] Purities were determined by ^1H NMR and LC-MS or GLC. [d] The product was recovered from the A-15 resin by washing with NH_3 in methanol. [e] Dashes indicate that the reaction was not investigated. [f] See text. [g] Oxidation was performed twice. [h] Yield not determined due to volatility of the compound. [i] Reaction was carried out in refluxing THF.

corresponding trifluoromethyl ketones with good yields and purity. The only exception was the nitro-substituted alcohol (2b) which generated a complex mixture in which no trace of the ketone could be found. A decrease in reactivity was observed when electron-withdrawing substituents were present on the aromatic ring, but complete conversions could still be obtained by performing the oxidation twice (2c-d) or by employing higher reaction temperatures (2k).

CONCLUSIONS

We have shown the feasibility of using polymer-supported reagents in the multi-step preparation of a number of trifluoromethyl substituted ketones in high yields and excellent purities *via* a two-step sequence involving no conventional chromatographic purification. It should be noted that many of the starting aldehydes could also be

obtained from alcohols by oxidation with polymer-supported oxidants [3]. Aldehydes are excellent precursors for a variety of multi-parallel synthesis programs and the new application reported above further illustrates the molecular diversity that is possible by batch splitting at intermediate synthesis stages during multi-step sequences using polymer-supported reagents.

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[12] Prepared by treating Amberlyst A-27 (Cl^- form) with an aqueous solution of potassium permanganate. The obtained brick-red material was washed with water and acetone followed by drying *in vacuo*. The use of freshly prepared resin is recommended. See also reference 5b.

[13] Recently we have found that activated MnO_2 (available from Aldrich; order No. 21,764-6) in refluxing CH_2Cl_2 can alternatively be used instead of A-27 (MnO_4^- form) in the oxidation of aromatic trifluoromethyl alcohols.

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