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Direct and Efficient One-Pot Preparation of Ketones from Aldehydes Using *N-tert*-Butylphenylsulfinimidoyl Chloride

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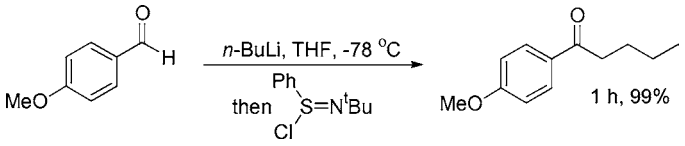
ABSTRACT



A general, one-pot process has been established to prepare ketones from aldehydes using *N-tert*-butylphenylsulfinimidoyl chloride. By employing the developed protocol, a range of unsymmetrical ketones has been prepared in good yields from aldehydes in one simple synthetic operation.

The broad reactivity profile of carbonyl compounds and their ready conversion to other functional groups make them a cornerstone of organic chemistry.[1] In this regard, the availability of both aldehydes and ketones is crucial to the preparative chemist. With respect to synthetic flexibility, the preparation of a ketone from an aldehyde is a synthetic transformation that often requires two steps, an alkylation followed by an oxidation, with rather few direct methods existing. The synthetic technologies known to carry out this valuable transformation include the use of organovanadium reagents,[2] magnesium-mediated addition/Oppenauer oxidation,[3] and a boron-Wittig process.[4] In addition, hydroacylation of alkenes[5] and transition metal-catalyzed cross-coupling[6] at elevated temperatures are useful in some cases, but these, like the aforementioned methods, remain limited in scope. The umpolung method of alkylation of dithianes[7] and subsequent unmasking of the carbonyl is often used but this overall procedure is less direct and requires a series of individual transformations. In contrast, the Stetter reaction offers a complementary and more practically direct umpolung-type approach.[8] While methods exist for the conversion of acid chlorides,[9] nitriles,[10] and Weinreb amides[11] to ketones, these methods generally require the preparation of these substrates and involve an overall change in oxidation level.

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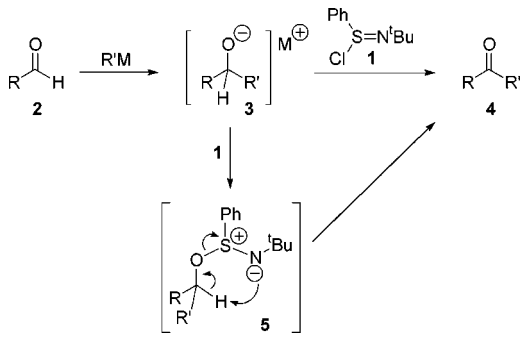
In 2000, Mukaiyama and co-workers reported on *N-tert*-butylphenylsulfinimidoyl chloride,[12] **1**, as a versatile oxidation reagent for use in organic synthesis.[13] In particular, this reagent can be employed in the oxidation of alcohols, amines, and hydroxylamines[13b,c] and in the dehydrogenation of ketones to enones under mild reaction conditions.[14] Recently, the Nicolaou group have applied this species in a dehydrogenation of a structurally complex ketone to an enone in their total synthesis of azaspiracid-1.[15] Additionally, Mukaiyama and co-workers have themselves employed their alcohol oxidation methodology with **1** in efforts toward the syntheses of taxanes.[16]

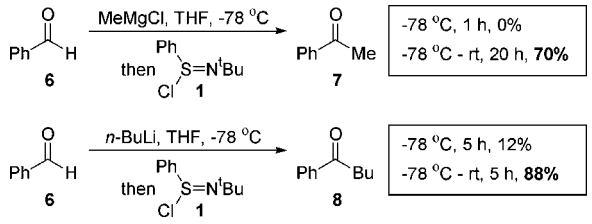
In attempts to expand the utility of the sulfinimidoyl chloride, **1**, recent work from our own laboratory[17] and from Matsuo and co-workers[18] has, independently, shown how this reagent can be employed in the formation of β-substituted enones from unsubstituted enones in a single, practical operation. Based on this, we envisaged that this same commercially available[19] reagent could be applied within a novel and general one-pot process to allow the expedient synthesis of ketones from aldehydes. This concept is depicted in Scheme 1. Specifically, we believed that the alkoxide **3**, derived from nucleophilic addition of an organometallic reagent to an aldehyde **2**, could react with **1** directly to afford the desired ketone **4**, via sulfinimidate intermediate **5**.

Scheme 1. Concept for a One-Pot Transformation from Aldehyde to Ketone, via Reaction between Intermediate Alkoxide **3** and **1**



Our first attempt at this one-pot transformation used benzaldehyde **6** with methylmagnesium chloride serving as the nucleophile (Scheme 2). The Grignard reagent was allowed to react with **6**, over 0.5 h at −78 °C, before addition of **1**. Following another 0.5 h at −78 °C, no desired product formation was observed. Undaunted, we made a second attempt with slight variations in procedure. In this case, the reaction was allowed to warm to room temperature with the reaction time, following addition of **1**, extended to 20 h. This minor change resulted in a 70% yield of acetophenone **7** and supported our initial reaction concept. At this stage we went on to apply an alkyllithium reagent, with the view that the resultant lithium alkoxide could react even more readily with sulfinimidoyl chloride, **1**.[20] In this case, *n*-butyllithium was added to benzaldehyde, followed by **1**, and after 5 h at −78 °C a 12% yield of valerophenone, **8**, was obtained. Analysis of the product mixture showed that 68% of 1-phenylpentan-1-ol had also been formed, indicating that alkylation had indeed occurred, and suggesting that the second stage of our reaction process was slow at low temperatures. To our delight, simply performing the reaction under the same conditions, but this time allowing the mixture to warm slowly to ambient temperature, afforded 88% of the desired ketone product.

Scheme 2. Initial One-Pot Aldehyde to Ketone Transformations; Preparation of Acetophenone **7** and Valerophenone **8** from Benzaldehyde **6**



A further brief program of optimization showed that the complete reaction sequence could be performed within 1 h: the nucleophile is added to the aldehyde in THF at −78 °C and the mixture stirred for 20 min, before addition of the electrophilic oxidant **1** (1.5 equiv); after a further 20 min at −78 °C, the reaction is allowed to warm over 20 min before final workup. Monitoring of the internal reaction temperature showed that this reached approximately 20 °C over this latter time period.

Using benzaldehyde **6** as the substrate with PhLi as the nucleophile, we also investigated changing the reaction solvent to diethyl ether or benzene. It was thus demonstrated that the reactions could also be performed in these alternative solvents, although THF appeared to provide the optimal results (Table 1, entries 1−3) and, more specifically, an excellent 93% yield of benzophenone, **9**. Additionally, a comparison study of the organometallic species used was

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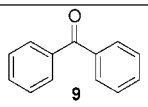
Table 1. Development of a One-Pot Process for Preparation of Ketones from Aldehydes[a]

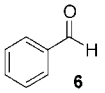
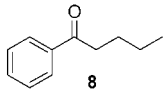
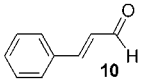
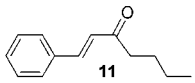
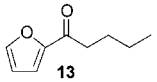
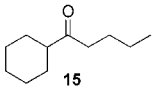
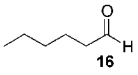
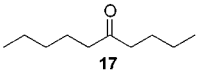
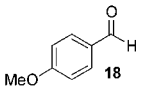
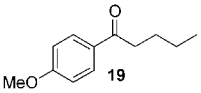
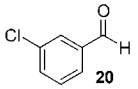
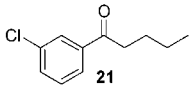
entry	R'M	product	solvent	yield (%)[b]
1	PhLi	 **9**	THF	93
2	PhLi	**9**	Et_2O	42
3	PhLi	**9**	PhH[c]	66
4	PhMgCl	**9**	THF	57
5	PhMgBr	**9**	THF	66

[a] Reactions were conducted with benzaldehyde **6** on a 2.0 mmol scale in 12 mL of solvent, under N_2. [b] Yield refers to isolated yield of purified products. [c] Reaction performed from 0 to 5 °C.

performed, evaluating PhMgCl and PhMgBr in addition to PhLi (Table 1). The results obtained indicated that the lithium reagent, rather than the corresponding magnesium compound, is more effective in these systems (yield of 93% vs 57−66% obtained with the Grignard reagents; Table 1, entries 1, 4, 5). On the basis of these investigations, two conclusions could be drawn. First, it is clear that these reactions are indeed fast (1 h), but only at temperatures above −78 °C, and second the readily available organolithium compounds exhibited the best profile as the nucleophile in terms of overall reaction efficiency. Armed with these important pieces of information, we proceeded to investigate the generality of this facile, one-pot transformation.

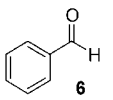
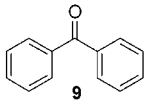
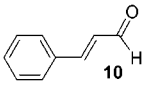
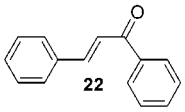
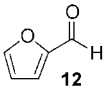
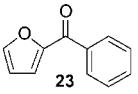
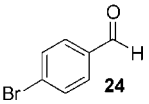
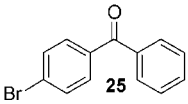
As shown in Table 2, this sulfimidoyl chloride-mediated oxidative process appears to be quite general to a range of substrates. Using *n*-butyllithium, this process was successfully applied to a range of aldehydes, including various (substituted) aromatic substrates (Table 2, entries 1, 6, 7), as well as α,*β*-unsaturated (*trans*-cinnamaldehyde, **10**), heteroaromatic (furfural, **12**), and primary and secondary aliphatic (entries 4 and 5) aldehydes. In each case the product was obtained in a good to excellent yield (49−99% isolated yield).[21,22] The lowest yield obtained was with the enolizable primary aliphatic substrate hexanal, **16**, whereas the secondary (cyclohexyl) aliphatic substrate gave 81% of the desired ketone, **15**. Both electron-rich and electron-deficient aryl aldehydes gave the expected products in high yield (entries 6 and 7). In a few examples the addition of DMPU as cosolvent proved to be beneficial (see, for example, Table 2, entry 3: no additive - 69%; 0.5 equiv of DMPU - 73%; 1 equiv of DMPU - 76%) with the increased Lewis basicity of DMPU presumably facilitating the reaction of the alkoxides with **1**. It is important to note that all reactions were performed over only 1 h and that the reaction appears to be tolerant of different substitution patterns and steric hindrance on the aldehyde. Furthermore, since the electrophilic reagent **1** is added as the final component within this overall process, there is no risk of over-alkylation of the products obtained to give undesired tertiary alcohols.

Table 2. Synthesis of Butyl-Substituted Ketones from Various Aldehydes by Reaction with *n*-Butyllithium and Subsequent in situ Oxidation with **1**[a]

entry	substrate	product	yield (%)[b]
1	 **6**	 **8**	88
2	 **10**	 **11**	80[c]
3	 **12**	 **13**	76[c]
4	 **14**	 **15**	81
5	 **16**	 **17**	49
6	 MeO **18**	 MeO **19**	99
7	 Cl **20**	 Cl **21**	70[c]

[a] Reactions were conducted on a 2.0 mmol scale in 12 mL of solvent, under N_2. All products exhibited satisfactory spectroscopic and physical properties. [b] Yield refers to isolated yield of purified products. [c] 1.0 equiv of DMPU added.

Table 3. Synthesis of Phenyl-Substituted Ketones from Various Aldehydes by Addition of Phenyllithium and Subsequent in situ Oxidation with **1**[a]

entry	substrate	product	yield (%)[b]
1	 **6**	 **9**	93
2	 **10**	 **22**	71
3	 **12**	 **23**	92[c]
4	 Br **24**	 Br **25**	79

[a] Reactions were conducted on a 2.0 mmol scale in 12 mL of solvent, under N_2. All products exhibited satisfactory spectroscopic and physical properties. [b] Yield refers to isolated yield of purified products. [c] 1.0 equiv of DMPU added.

Following the success observed with the addition of an alkyllithium reagent, we next investigated adding a different organolithium species, this time employing a commercially supplied solution of phenyllithium. A similar range of substrates was studied (Table 3), following the same general reaction protocol. The expected ketone products were obtained in good to excellent yields (71 −93% isolated yield) following purification. Overall, these results again illustrate the effectiveness of this technique in the preparation of a wide range of unsymmetrical ketones in one simple reaction process. Despite specific examples not being shown here, it is worth noting that, as previously observed, lower yields were obtained with the enolizable, aliphatic aldehydes. Having stated this, these reactions were performed using the same simple protocol as in each of the other examples, and work is currently ongoing in our laboratory in attempts to mildly modify the reaction conditions in order to allow these specific interconversions to be performed more effectively. In this regard, it is important to note that, when using isolated alcohols with reagent **1**, Mukaiyama has obtained high yields of the corresponding carbonyl compounds, and this is the case even with aliphatic alcohols.[13] Consequently, this would suggest that it is, indeed, the organolithium-mediated addition step that is leading to the lowered yields in these cases and not the subsequent oxidation process.

In conclusion, we have developed a one-pot process for the direct transformation of aldehydes to ketones. The process has been shown to be applicable to a range of both aldehyde substrates and organometallic reagents. Since the present reaction requires only commercial or readily available reagents, and taking into account the simple experimental protocol employed, we believe that this transformation will be of appreciable use to the synthetic community.

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Supporting Information Available: Experimental procedures, spectral details, and copies of ^{1}H and ^{13}CNMR spectra for all product compounds. Ths material is available free of charge via the Internet at http://pubs.acs.org.

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(21) **Representative Procedure.** To a flame-dried 25-mL round-bottomed flask, under nitrogen, was added *p*-anisaldehyde, **18** (272.3 mg, 2.0 mmol, 1.0 equiv), and dry THF (10 mL). This solution was cooled to −78 °C and stirred for 10 min before the dropwise addition of *n*BuLi (1.0 mL, 2.2 M in hexanes, 2.2 mmol, 1.1 equiv) over 0.5 min. The solution was allowed to stir at −78 °C for 20 min before a solution of **1** (647.2 mg, 3.0 mmol, 1.5 equiv) was added by syringe in THF (2 mL) over 1 min. The resultant yellow solution was stirred at −78 °C for 20 min, then allowed to warm to rt over 20 min, and then quenched by the addition of 2 M HCl (10 mL). The reaction was diluted with Et_2O (40 mL), the phases were separated, and the organic layer was washed with 2 M HCl (2 × 20 mL). The aqueous layer was back-extracted with Et_2O (2 × 15 mL), and the combined organic phase was then washed with water (40 mL) and brine (40 mL) and then dried over anhydrous Na_2SO_4 and concentrated, yielding a crude oil. Purification was carried out by column chromatography on silica gel, eluting with light petroleum ether and then 20:1 petroleum ether/diethyl ether to yield 1-(4-methoxyphenyl)pentan-1-one, **19**,[22] as a clear, colorless oil, 380.9 mg, 99%. IR (film) υ_{max} = 3071, 2958, 2872, 1676, 1601, 1576, 1509, 1464, 1311, 1258, 1170, 1031, 975, 841, 812, 759, 633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (2H, d, J = 8.9), 6.94 (2H, d, J = 8.9), 3.88 (3H, s), 2.92 (2H, t, J = 7.4), 1.72 (2H, pentet, J = 7.4), 1.41 (2H, sextet, J = 7.4), 0.96 ppm (3H, t, J = 7.4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5 (C═O), 163.5, 130.5 (two signals), 113.9, 55.7, 38.2, 27.0, 22.8, 14.1 ppm.

(22) Harada, T.; Ohno, T.; Kobayashi, S.; Mukaiyama, T. *Synthesis* **1991**, 1216.