Synthesis of 3-substituted 2-cyclohexenones through umpoled functionalization

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Abstract
A new protocol to obtain 3-substituted 2-cyclohexenones, was developed by reversing the chemical reactivity of 2-cyclohexenone. One-pot synthesis of 3-substituted 2-cyclohexenones can be achieved by treatment of 3-phenylthiosilyl enol ether with a mixture of t-BuLi/HMPA that allows hydrogen-selective exchange in presence of reactive electrophiles such as aldehydes, ketones and alkyl halides. This affords the corresponding product in moderate overall yield, after silyl enol ether cleavage and concomitant thiophenol elimination initiated with TBAF.

Introduction
The development of new methods for the efficient construction of organic molecules continues to be essential for accessing natural products and their structural analogues. In this context, the concept of umpolung or polarity inversion is associated with a temporal masking of a functional group to reverse its polarity and perform secondary reactions that would otherwise not be possible.1–3 Since retrosynthetic analysis was pioneered by E. J. Corey and co-workers in the early 1970s,4 the umpolung approaches attracted more attention because it enables the usage of a wider variety of starting materials for building complex natural products. From the perspective of natural product synthesis, little is known about 2-cyclohexenone, a cheap and widely available compound with great synthetic potential. 2-cyclohexenone has been used to synthesize highly valuable molecules, such as antimalarial-drug (+)-artemisinin,5 an example of an umpolung strategy was described in a protocol for insertion of side chains at the 3-position of the 2-cyclohexenone allowed the formation of epoxyquinol analogues.6 For this reason, 3-substituted 2-cyclohexenones 4are highlighted as recurrent building blocks for many purposes. They can be accessed through the umpolung reactivity of 2-cyclohexenone by means of its synthetic equivalents such as 1,3-bis(phenylthio)cyclohex-1-ene,7 3-cyanocyclohexanone,8 1-dioxo lanlyl-3-toslylcyclohexane,9 or (3-(tert-butyldimethylsiloxy) cyclohex-2-en-1-yl)triphenylphosphonium triflate.10–12 These methods required multi-step transformations and overall yields are moderate.

An interesting and practical methodology to achieve the 3-electrophilic substitution of 2-cyclohexenone was reported by Katritzky's group in 1995.13 It consisted in the reaction between 2-cyclohexenone and trimethylsilylbenzotriazole to generate a 1,4-adduct similar to compound 2b. Treatment of this non-isolated-intermediate with LDA promoted the formation of an allylic anion which was then trapped by an electrophile. Subsequent addition of aqueous acid obtained the corresponding 3-substituted 2-cyclohexenones 4 (yields 50–75%).

On the other hand, Evans demonstrated in 1977 that (phenylthio)trimethylsilane14,15 can be used as a protecting group of aldehydes and 𝛼, 𝛽-unsaturated carbonyls due to the high affinity between silicon and oxygen atoms. Interestingly, the 1,4-adduct 2a that arises from the reaction between 1a and 2-cyclohexenone is also air-labile. Therefore, we thought that a more stable analogue such as (phenylthio)triisopropylsilane1b might afford an analogue of 2a which also would undergo a 3-electrophilic substitution after its treatment with a base. Finally, TBAF would trigger a one-pot transformation of corresponding intermediates 3 into 3-substituted 2-cyclohexenones 4 as described in Scheme 1.

Results and discussion
The (phenylthio)sesilanes 1 were prepared using Davis' protocol.16 It involves a condensation between thiophenol and corresponding trialkylsilyl chloride in presence of Et3N. While triisopropyl 1b and tert-butylidimethyl 1c derivatives were isolated

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In yields of 80% and 54% respectively, the (phenylthio)trimethylsilane 1a was unstable during the heating process for vacuum distillation (Scheme 2).16b

With compounds 1b and 1c at hand, we proceeded to find the best reaction conditions for generating 1,4-adducts 2 (Table 1). In the first experiment, a neat equimolar mixture of 2-cyclohexenone and (phenylthio)trisopropylsilane 1b did not afford any product 2b after stirring for 2 h even in the presence of potassium cyanide-18-crown-6 complex 17 (0.3% mol) as initiator (Entry 1). These conditions were reported by Evans to produce 1,4-adducts.14,15 However, an increase in the reaction time to 18 h resulted in the desired compound 2b, but with a poor yield of 21% (Entry 2). Moreover, when the amount of the anionic initiator was increased by 5 times with a reaction time of 2 h, the yield was slightly improved to 28% (Entry 3). Interestingly, carrying out the reaction in THF, while applying 0.9%-mol of the complex, 18 h), provided a moderate yield of compound 2b (37%, entry 4). In all these experiments only the starting material 2b was recovered. We believe that the reason for which the acid-base reaction did not happen was due to the short half-life time that n-BuLi exhibits in THF at -78 °C.18,19 Likewise, the proton abstraction by the base on the sulfide 2b was not accomplished when Et2O was used instead of THF. Nor was it achieved by applying a much stronger base such as t-BuLi at 0 °C. It is known that the presence of TMEDA or HMPA as additives has an important effect on the generation and stabilization of the respective carbanions.20 Consequently, when experiments were carried out at 0 °C in the presence of TMEDA using benzaldehyde as an electrophile, it was evident that the β-lithiation reaction took place in the thio-phenyl ring instead of the α-lithiation reaction of the sulfide-side of 2b because the alcohol 8 was isolated (Fig 1). It is worth noting that at -78 °C the directed α-metalation of 2b did not occur in THF. The finding that TMEDA readily promotes the β-lithiation increased expectations for positive outcomes by using HMPA. Gratifyingly, when the reaction was carried out in THF/HMPA (2.5 equiv) at -78 °C, the expected anion of sulfide 2b was consumed by PhCHO, resulting in intermediate 3a. The crude product 3a went through a slow one-pot process of deprotection/β-elimination when TBAF was added, and ultimately led to the isolation of 2-cyclohexenone 4a with a yield of 71% (Table 2, entry 1). This umpolung strategy was expanded when derivatives 4b–h were synthesized using m-anisaldehyde, piperonal, acetophenone, chloromethyl pivalate, benzyl bromide, 2-cyclohexenone and paraformaldehyde as electrophiles (Table 2). Hence, the procedure could be applied to ketones (Entry 4), alkyl halides (Entries 5–6) and even α,β-unsaturated compounds such as 2-cyclohexenone (Entry 7). Here it is worth mentioning that this methodology comprises two continuous reactions in a single step, therefore yields are acceptable.

Aldehydes showed unusual behavior and exhibited a poor performance (Entries 2 and 3) especially paraformaldehyde (entry 8). We believe that low yields are due to an isomerization/oxygenation process that happened, especially for 2-cyclohexenones 4a and 4h in a slightly acidic or basic media. For example, when 2-cyclo-
hexenones 4a or 4h remained dissolved in CDCl₃ for a long time, the formation of compounds 7a and 7h was observed (Scheme 3). Apparently, delocalization of the electron density in the α,β-unsaturated system would allow tautomeration to bis-enol intermediates. Then, the keto-enol equilibrium would stimulate the keto-enol tautomeration (1.0 equiv), HMPA (2.5 mol %) was added dropwise. In summary, we have developed a novel and direct methodology for the preparation of 3-substituted 2-cyclohexenones 4b employing an umpolung strategy. The versatility and potential this methodology possess is revealed by the use of a variety of electrophilic species, notably the cheap and widely available 2-cyclohexenone, to generate in one-pot process 3-substituted 2-cyclohexenones 4 which could serve as useful building blocks to synthesize highly valuable molecules. Further investigation in this area is being carried out in our laboratory.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.07.007.

References

(b) Synthesis of phenyl(trialkylsilyl)sulfides 1b and 1c. To a solution of thiophenol (1.0 equiv) and the corresponding trialkylsilyl chloride (1.1 equiv) in anhydrous THF [1.95 M], under nitrogen atmosphere, triethylamine (1.2 equiv) dissolved in anhydrous THF [2.37 M] was added dropwise. Immediately the triethylammonium chloride is observed as a white solid. After stirring for 18 h at room temperature, the reaction mixture was filtered through colone, the filter was washed with 10 mL of THF, and the filtrate was washed with 10 mL of an aqueous solution of KOH (10%) in order to eliminate the excess of thioenol. The organic layers were dried over Na₂SO₄ and evaporated in vacuo. The crude reaction was then distilled under reduced pressure affording the corresponding phenyl(trialkylsilyl)sulfide 1b. Compound 1b: The general procedure was applied using 1.0 mL of thiophenol (1.073 g, 9.74 mmol), 2.3 mL of TIPSiCl (2.072 g, 10.75 mol) in 5 mL of anhydrous THF. This reaction afforded 2.07 g (80%) of 2b as a colorless oil. TLC-R₆₅ (Hexanes 100%) 0.62, bp 109 °C (9.0 mmHg); NMR-¹H (300 MHz, CDCl₃) δ 7.50 (dd, J = 6.5, 3.0 Hz, 2H), 7.24–7.18 (m, 3H), 1.25 (dd, J = 15.6, 13.0 Hz, 1H), 1.09 (d, J = 7.1 Hz, 18H); NMR-¹C (75 MHz, CDCl₃) δ 135.4, 131.5, 128.5, 126.6, 18.4, 13.1. Mass spectrum m/z [M+] 266, 223 (100%). Compound 1c: The general procedure was applied using 1.0 mL of thiophenol (1.073 g, 9.74 mmol), 1.173 g (54%) of 1c as a colorless oil. TLC-R₆₅ (Hexanes 100%) 0.55, bp 90 °C (9.0 mmHg); NMR-¹H (300 MHz, CDCl₃) δ 7.25 (dd, J = 6.6, 3.0 Hz, 2H), 7.08–7.01 (m, 3H), 0.80 (s, 9H), –0.09 (s, 18H); NMR-¹C (75 MHz, CDCl₃) δ 135.6, 131.5, 128.6, 126.8, 26.4, 19.0. –3.3. Synthesis of 3-phenylthio-1-(trialkylsilyl)cyclohex-1ene 2: The KCl/18-crown-6 complex was added to a well-stirred solution of 2-cyclohexenone (1.0 equiv) and the respective phenyl(trialkylsilyl)sulfide 1b (1.0 equiv) in freshly distilled dry THF [1.6 M]. Stirring under nitrogen atmosphere at room temperature was continued for 18 h and the yellow solution was concentrated in vacuum and the products were obtained as oils and used in their crude form. Compound 2b: The general procedure was applied using 376 mg of 2-cyclohexenone (3.91 mmol), 1.24 g of 1b and 12 mg of KCl/18-crown-6 complex (0.04 mmol) in anhydrous THF (2.5 mL). The reaction crude was purified by column chromatography (4.0 × 10.0 cm. silica gel; Hexanes 100%), affording 847 mg (60%) of 2b as a yellow pallid oil. TLC-R₆₅