Selective Metal-Free Deoxygenation of Unsymmetrical 1,2-Dicarbonyl Compounds by Chlorotrimethylsilane and Sodium Iodide

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A Selective Metal-Free Deoxygenation of Unsymmetrical 1,2-Dicarbonyl Compounds by Chlorotrimethylsilane and Sodium Iodide

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Supporting Information Placeholder

ABSTRACT: For the first time, the combination of chlorotrimethylsilane (TMSCI) with NaI is used as a selective reducing system towards 1,2-diketones. This combination is successfully evaluated with several unsymmetrically benzil derivatives, which are reduced in good yields and with a total α-regioselectivity at room temperature. Identification of benzoin intermediates is achieved and a mechanistic radical process is proposed.

It is well-established that trimethylsilyl iodide (TMSI), in which silicon atom acts as a hard acid and iodide as a soft base, is a useful and powerful reagent in organic synthesis. TMSI reacts with oxygen-containing compounds forming a strong silicon-oxygen bond. The iodide then acts as a strong nucleophile in a subsequent displacement step, thus resulting in cleavage of carbon-oxygen bonds. Typical applications of this reagent are the cleavage of ethers or carboxylic esters, conversion of ketals into carbonyl compounds, and alcohols into iodide derivatives. Most of these transformations occurred through an ionic mechanism. Although ketones readily react with TMSI to provide enol silyl derivatives, to our knowledge, except deoxygenation of sulfoxides into sulfides, nothing is known about the ability of TMSI to act as a reducing agent with carbonyl compounds.

Carbonyl reduction is among the most important and prevalent reactions in organic synthesis, and both industry as well as academia place special emphasis on this transformation due to its versatility for the generation of a wide range of products. In this context, the deoxygenation of ketones to methane derivatives is also an essential process in organic chemistry. Although relatively uncommon in process chemistry, the reductive mono deoxygenation of 1,2-dicarbonyl compounds into mono-ketone derivatives has also been reported, but preparative methods that may drive these reactions selectively have been seldom optimized in the past. To accomplish this transformation, the use of catalytic hydrogenation in the presence of Ni(0) complexes and metal-based reducing agents (TiCl4/Zn, SmI2) comprise most examples, but metal-free procedures (HI/AcOH and H2S/py) have also been reported. From a large-scale preparative point of view, these protocols suffer from many drawbacks including the use of flammable gas (H2 or H2S), the frequent need for specialized equipment, the requirement of harsh reaction conditions, and the low functional group tolerance (chemo- and regioselectivity issues) which limit their application in poly-functionalized substrates. Therefore, the availability of a mild, simple, safe, chemo- and easy-to-handle reducing agent is of special interest because it allows the formation of complex organic target molecules without the need for wasteful protection/deprotection steps. Herein, we report a highly efficient regioselective reduction of 1,2-diarylketone derivatives using the couple chlorotrimethylsilane (TMSCI)/NaI in methylene chloride.

Scheme 1. Regioselective reduction of 1a by TMSCI/NaI in CH2Cl2 at rt.

Initially, we had to investigate the other cleavage of benzil derivative 1a in CH2Cl2 using an excess of TMSCI/NaI combination at room temperature (Scheme 1). Contrary to our expectation, the reaction did not afford the desired phenol derivative. We serendipitously discovered that, under these mild conditions, if the 4-MeO group remained unchanged, one of the two carbonyl functions (Cox=O) of benzil 1a was totally reduced to the α-deoxybenzoin (DOB) α-2a as a single product (97%) with a total α-regioselectivity. A similar yield of α-2a (95%) was obtained when achieving this reaction under anhydrous conditions (oven-dried NaI and distillation of TMSCI and
CH$_3$Cl$_2$ over CaH$_2$ prior to use). This result suggests that traces of HCl in technical TMSCl or traces of moisture in the solvent have no influence on the outcome of the reducing properties of the TMSCl/NaI combination. To understand this unexpected selective reduction, we initially investigated the reaction of 1a in CH$_2$Cl$_2$ with different combinations of silicon species and solvents. First, we observed that the reduction process of 1a did not occur with TMSCl alone, 1a was recovered unchanged even when achieving the reaction at 40 °C. Replacing TMSCl/NaI combination by TMSI allows the reaction to occur providing α-2a, but with a lower yield of 65%. Next, we focused our attention on the sources of silicon species in the presence of NaI in this process. With TMSOTT, no reaction occurred whereas, SiCl$_4$ led to α-2a in a modest 65% yield, along with unidentified by-products. However, we were pleased to observe that the regioselective reduction of 1a was still efficient using Ph$_3$SiCl (97%) or (EtO)$_2$SiCl (87%) in place of TMSCl, but required 10 equiv of the (EtO)$_2$SiCl/NaI combination. The nature of the additive salt was also studied and no reduction of 1a occurred when replacing NaI by NaBr, clearly indicating that the iodide counter ion is important in this reaction. Because TMSI fumes in air and should be prepared freshly, distilled and immediately used on the contrary of TMSCl, we have chosen to take advantage of this easy to handle and inexpensive TMSCl/NaI combination to reduce benzil derivatives 1. Screening with respect to the solvents was next carried out. No reduction reaction occurred in protic polar solvents (e.g., MeOH, EtOH or iPrOH) at rt, and 1a was recovered unchanged. The use of aprotic polar solvent (e.g., CH$_2$CN), resulted in a sluggish reaction and 2a was isolated with a modest 50% yield after 18 h of reaction. Among the solvents studied, CHCl$_3$, CCl$_4$ or toluene have proven to be effective as CH$_2$Cl$_2$, providing α-2a with nearly quantitative yields. Several control experiments were achieved, as suggested by the referees, to prove that the TMSCl/NaI combination is the reducing system rather than small amounts of HI= formed between TMSCl/NaI and traces of water present in the solvent. Thus, when performing the reduction of 1a in CH$_2$Cl$_2$ at rt for 24 h with 0.5, 2 or 10 equiv of aqueous HI (wt 57%), no reduction occurred. Increasing the amount of HI to 15 equiv, resulted in a mixture in which the expected α-2a was formed in less than 15%. All of these results strongly confirm that the novel reducing agent TMSCl/NaI is responsible for this transformation, discarding definitively the HI hypothesis.

After optimizing the experimental conditions with 1a and TMSCl/NaI combination (5 equiv) in CH$_2$Cl$_2$, the scope of this reduction reaction was explored with several other benzil 1b−y. As shown in Table 1, a variety of functional groups was well tolerated to give rise to the desired α-DOB 2 with good to excellent yields. Examination of results showed that a total α-regioselectivity was observed for several benzils having an electron donating group (EDG) on ortho- and para-position. This regioselective reduction was also effective with a para free-phenol derivative providing DOB α-2h with a high 89% yield. One note that α-2h was also obtained from other benzil derivatives bearing on the 4-position a -OMOM (α-2h, 50%), -OTBS (α-2h, 84%), -OBn (α-2h, 67%), and -OAc (α-2h, 80%) function. For p-ethoxy carbonylbenzil substrate, the reactivity of the diketone significantly decreased, leading to a complex mix-ture with no trace of DOB 2l. However, push-pull benzil derivatives were successfully and regioselectively reduced into the desired α-DOB 2m-t with excellent yields. At least, an example of reduc-

duction of a push-pull α-diketone is described, and as expected, DOB 2y was obtained as a regioisomeric mixture of monoketones (α-2y/β-2y = 84/16), indicating that the reduction takes place preferentially on the carbon atom proximal to the more electron-rich ring. To propose a plausible mechanism of this regioselective reduction process of α-diketones, we next isolated the benzoin intermediates by quenching the reaction with H$_2$O after reduced reaction times and/or temperature (Scheme 2). The reduction of benzils 1a and 1b was achieved at - 40 °C for 15 min whereas the reduction of quinoline derivative 1x required 2.5 h of reaction at rt.

**Table 1: Functional groups tolerance**

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<thead>
<tr>
<th>Ar$^1$</th>
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<th>α-2</th>
<th>Yield (%)</th>
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<tr>
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<td>Ph</td>
<td>α-2b</td>
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<td>3-MeOPh</td>
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<td>Ph</td>
<td>α-2d</td>
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<td>Ph</td>
<td>α-2f</td>
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<td>α-2g</td>
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<td>4-MePh</td>
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<td>98$^f$</td>
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</table>

$^a$Typical reaction conditions: a mixture of benzil 1 (1 mmol) and NaI (5 mmol) was stirred in CH$_2$Cl$_2$ for 5 min. Then, 5 mmol of TMSCl were added to solutions which was stirred until completion (judged by TLC).

$^b$Nd not determined.

$^c$Obtained as an inseparable mixture of α-2d/β-2d = 88:12.

$^d$Experiment was achieved in refluxing CHCl$_3$.

$^e$Obtained as a separable mixture of α-2w/β-2w = 90:10.

$^f$Obtained as an inseparable mixture of α-2y/β-2y = 84:16.

**Scheme 2. Synthesis of DOBs 2 via their benzoin intermediates.**

(a) For 1a and 1b the reaction was achieved at - 40 °C for 15 min; for 1x the reaction was carried out at rt for 2.5 h. In all cases and to our surprise, the reduction of these benzils proceeded overwhelmingly on the Cβ of diketones studied, to furnish mainly β-benzizons 3a and 3b and exclusively β-3x with good to excellent yields.12
One can note that a less marked β-regioselectivity has been previously reported with very few examples of unsymmetrical benzils using other reducing agents such as alkylphosphines, baker’s yeast, and NADH models. Next, the reduction of benzils 3a,b and β-3x was attempted under the conditions previously reported in Table 1. To our delight, a “reverse” Cα-reduction occurred invariably to furnish the previously obtained α-DOBs 2a,b and α-2x in good yields, and with no trace of β-DOBs regioisomers.

Scheme 3. Plausible mechanism for the regioselective reduction of benzil 1a into DOB α-2a using TMSCI/NaI combination in CH₂Cl₂

We next studied the spectroscopic data of the TMSCI/NaI combination by ¹H and ¹³C NMR in CD₂Cl₂. Under argon, a solution of equimolar proportions of NaI and TMSCI in CD₂Cl₂ furnished a colorless solution with absorptions at δ ¹H 0.37 ppm and δ ¹³C 1.34 ppm, rigorously identical with those of TMSCI alone (see ESI, Figure 1). On the contrary, TMSI in CD₂Cl₂ led to a pink-purple solution with different absorptions at 0.73 and 3.73 ppm. These observations strongly suggest that TMSI is not formed in methylene chloride by the combination of TMSCI with NaI, in agreement with Olah’s report.

To explain this unusual regioselective reduction of benzils 1 by the TMSCI/NaI combination in CH₂Cl₂, a plausible radical mechanism is proposed in Scheme 3. The reductive process begins probably by a coordination between oxygen atoms of 1a with TMSCI followed by a nucleophile addition of NaI on the carbonyl functions giving intermediates α-I and β-I. Then a radical fragmentation occurred on I to give siloxy ketone radical of type α-II and β-II or their mesomeric forms α-III and β-III. Further reaction of III in the presence of TMSCI and NaI would furnish the intermediate IV and I₂, which coloured the methylene chloride solution in brown. Next, an additional equivalent of TMSCI would coordinate on the oxygen atom proximal to the electron-rich ring. The resulting intermediate V can lose TMSTMS with the help of the MeO substituent to furnish species VI, thus explaining the regioselectivity of this reducing process. All our attempts to isolate TMSTMS were unsuccessful however, when using Ph₃SiCl instead of TMSCI, Ph₃SiOSiPh₃ was successfully isolated after hydrolysis, reinforcing our ideas on this mechanism. A subsequent iodide atom addition on VI would give the alkanyl intermediate VII. After hydrolysis, the resulting enol VIII would react with NaI to provide α-iodoketone IX which was reduced into 2a by an iodide. To support this mechanistic hypothesis, incorporation of deuterium atoms into 2a in separate experiments was tried. No D₂-labelled 2a was observed when using CD₂Cl₂ or TMSCI(D₂). On the contrary, when 1a was reacted with TMSCI/NaI in CH₂Cl₂, hydrolysis with D₂O, allowed incorporation of two deuterium atoms on Cα of 2a. To confirm that this selective transformation proceeded through a radical process rather than an anionic mechanism, 1z having an o-allyl substituent, in which the terminal olefin would trap radical species, was reacted with TMSCI/NaI in CH₂Cl₂ (Scheme 4). Accordingly, a cyclized product 4 was isolated after hydrolysis in 21% yield, together with unidentified by-products. This result strongly supports the radical mechanism depicted in Scheme 3.

Scheme 4. Reaction of 1z with TMSCI/NaI combination in CH₂Cl₂ at rt

Because deoxybenzoins are important structural moieties that occur in bioactive molecules, it is now possible to have a rapid and efficient access to the corresponding α- and β-DOBs 2 starting from a single diarylalkyne using two different pathways...
(Scheme 5). As an illustration, diarylalkynes 5a-c were successfully transformed into β-2g, β-2n and β-2p after a regioselective metal-free hydration of the triple bond in the presence of a catalytic amount of PTSA in EtOH using a protocol developed in our group.22 On the other hand, diarylalkynes 5a-c were readily oxidized into their corresponding benzil derivatives 1g, 1n and 1p using DMSO23 in the presence of catalytic amounts of PdCl2. The reduction of these benzils by the TMSCl/NaI system, which was discussed above, led rapidly and efficiently to the corresponding DOBs α-2g, α-2n and α-2p with good yields and with a total α-regioselectivity.

In summary, we have demonstrated for the first time that the TMSCl/NaI combination in CH2Cl2 is a highly efficient reducing system of unsymmetrical benzil derivatives. The easy to handle protocol developed herein provides a facile, rapid and regioselective access to DOBs α-2 at rt with no need of any hazardous reagents or expensive metals. The reduction takes place invariably on the carbonyl proximal to the more electron rich aromatic ring. Since sustainable development is now a real place invariably on the carbonyl proximal to the more electron rich aromatic ring. Since sustainable development is now a real challenge for the chemical industry, we think that this eco-friendly metal-free reduction is an important contribution in this field.

ASSOCIATED CONTENT

Supporting Information
Experimental procedure, NMR spectra, and analytical data for all new compounds (PDF)

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Author Contributions
†These authors contributed equally.

Notes
The authors declare no competing financial interest.

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REFERENCES

(9) Identification of α-2a was determined by COSY, NOESY, HMBC and HSCQ experiments.
(10) When 1a was treated by HI (wt 57%) in refluxing AcOH according to Fuson’s conditions (ref. 8b), 2b was obtained (89%) indicating that a demethylation occured to provide a phenolic species.
(11) 1H NMR results revealed that the crude consists of a mixture of α-2a/β-3a/α-2b in a 15/57/10 ratio.
(12) Identification and ratio of regiosomers α-3a/β-3a was determined by COSY, NOESY, HMBC and HSCQ experiments on the crude mixture.
(16) After hydrolysis, the brown I mixture was discolored by a saturated Na2S2O3 solution.
(19) In the media of the TEMPO, a radical scavenger, completely inhibited the reducing process of the benzil derivative 1a.
(20) Since a radical mechanism was supported by the transformation of 1a into 4, we discarded the formation of intermediate IV through a reaction of α-4 or β-4 with an iodine atom.