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

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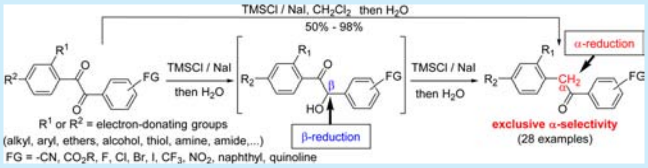
S Supporting Information

ABSTRACT: For the first time, the combination of chlorotrimethylsilane with NaI is used as a selective reducing system toward 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.

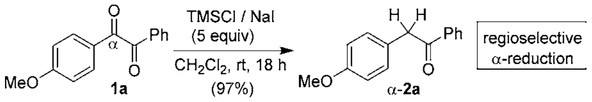


It is well-established that trimethylsilyl iodide (TMSI), in which the silicon atom acts as a hard acid and iodide as a soft base, is a useful and powerful reagent in organic synthesis.[1] TMSI reacts with oxygen-containing compounds to form a strong silicon−oxygen bond. The iodide then acts as a strong 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 and 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 ethers,[2] to our knowledge, except deoxygenation of sulfoxides into sulfides,[3] 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.[4] In this context, the deoxygenation of ketones to methylene derivatives is also an essential process in organic chemistry.[5] Although relatively uncommon in process chemistry, the reductive mono-deoxygenation of 1,2-dicarbonyl compounds into monoketone 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[6] and metal-based reducing agents ($TiCl_4$/Zn, SmI_2)[7] comprises most examples, but metal-free procedures (HI/AcOH and H_2S/py)[8] have also been reported. From a large-scale preparative point of view, these protocols suffer from many drawbacks, including the use of flammable gas (H_2 or H_2S), the frequent need for specialized equipment, the requirement of harsh reaction conditions, and low functional group tolerance (chemo- and regioselectivity issues), which limit their application in polyfunctionalized substrates. Therefore, the availability of a mild, simple, safe, chemoselective, 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 (TMSCl)/NaI in methylene chloride.

Initially, we had to investigate the ether cleavage of benzil derivative **1a** in CH_2Cl_2 using an excess of TMSCl/NaI combination at room temperature (Scheme 1). Contrary to our expectations, 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 ($C\alpha = O$) of benzil **1a** was totally reduced to produce the α-deoxybenzoin (DOB) α-**2a**[9] as a single product (97%)[10] with a total α-regioselectivity. A similar yield of α-**2a** (95%) was obtained when this reaction was achieved under anhydrous conditions (oven-dried NaI and distillation of TMSCl and CH_2Cl_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

Scheme 1. Regioselective Reduction of 1a by TMSCl/NaI in CH_2Cl_2 at rt



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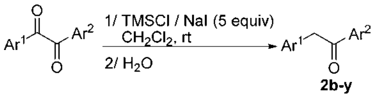
reaction of **1a** in CH_2Cl_2 with different combinations of silicon species and salts. First, we observed that the reduction process of **1a** did not occur with TMSCl alone; **1a** was recovered unchanged even when the reaction was achieved at 40 °C. Replacing the TMSCl/NaI combination by TMSI allows the reaction to occur to provide *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 TMSOTf, no reaction occurred, whereas $SiCl_4$ led to *α*-**2a** in a modest 65% yield along with unidentified byproducts. However, we were pleased to observe that the regioselective reduction of **1a** was still efficient using Ph_3SiCl (97%) or $(EtO)_3SiCl$ (87%) in place of TMSCl but required 10 equiv of the $(EtO)_3SiCl$/NaI combination. The nature of the additive salt was also studied, and no reduction of **1a** occurred when NaI was replaced by NaBr, clearly indicating that the iodide counterion is important in this reaction. Because TMSI fumes in air and should be prepared freshly, distilled, and immediately used, contrary to 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 *i*PrOH) at rt, and **1a** was recovered unchanged. The use of aprotic polar solvent (e.g., CH_3CN) 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 been proven to be effective as CH_2Cl_2, providing *α*-**2a** with nearly quantitative yields. Several control experiments were achieved, as suggested by the reviewers, to prove that the TMSCl/NaI combination is the reducing system rather than small amounts of HI[8a−c] formed between TMSCl/NaI and traces of water present in the solvent. Thus, when the reduction of **1a** was performed in CH_2Cl_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%.[11] All of these results strongly confirm that the novel reducing agent TMSCl/NaI is responsible for this transformation, discarding definitively the HI hypothesis.

After the experimental conditions with **1a** and TMSCl/NaI combination (5 equiv) in CH_2Cl_2 were optimized, the scope of this reduction reaction was explored with several other benzils **1b**−**y**. As shown in Table 1, a variety of functional groups was well tolerated to give rise to the desired *α*-DOBs **2** with good to excellent yields. Examination of the results showed that a total *α*-regioselectivity was observed for several benzils having an electron-donating group (EDG) on the *ortho*- and *para*-positions. This regioselective reduction was also effective with a *para* free-phenol derivative providing DOB *α*-**2h** with a high 89% yield. It should be noted 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*-ethoxycarbonylbenzil substrate, the reactivity of the diketone significantly decreased, leading to a complex mixture with no trace of DOB **2l**. However, push−pull benzil derivatives were successfully and regioselectively reduced into the desired *α*-DOBs **2m**−**t** with excellent yields. An example of reduction of a push−push *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_2O 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 Group Tolerance[a]

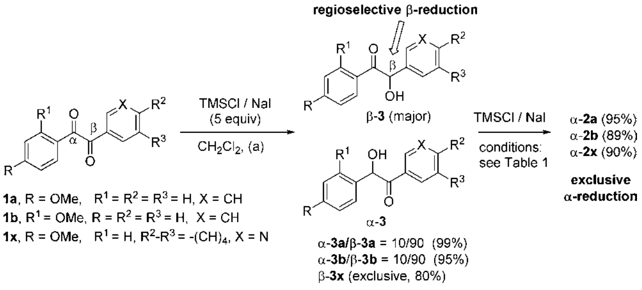


Ar^1	Ar^2	*α*-2	yield (%)
2-MeOPh	Ph	*α*-**2b**	98
3-MeOPh	Ph	*α*-**2c**	nd[b]
4-MePh	Ph	*α*-**2d**	78[c]
4-MeSPh	Ph	*α*-**2e**	95
4-(4′MeOPh)Ph	Ph	*α*-**2f**	83[d]
4-(4′*t*-BuPh)Ph	Ph	*α*-**2g**	79[d]
4-HOPh	Ph	*α*-**2h**	89
4-*i*PrOPh	Ph	*α*-**2i**	97
4-H_2NPh	Ph	*α*-**2j**	61
4-AcNHPh	Ph	*α*-**2k**	79
4-MeO_2CPh	Ph	*α*-**2l**	0
4-MeOPh	4-O_2NPh	*α*-**2m**	80
4-MeOPh	4-EtO_2CPh	*α*-**2n**	96
4-MeOPh	4-BrPh	*α*-**2o**	97
4-MeOPh	4-IPh	*α*-**2p**	73
4-MeOPh	4-FPh	*α*-**2q**	88
4-MeOPh	2-IPh	*α*-**2r**	57
4-MeOPh	4-F_3CPh	*α*-**2s**	95
4-MeOPh	2-FPh	*α*-**2t**	98[d]
4-MeOPh	3-CO_2EtPh	*α*-**2u**	96
4-MeOPh	3-NCPh	*α*-**2v**	60
4-MeOPh	2-naphtyl	*α*-**2w**	80[d,e]
4-MeOPh	3-quinolyl	*α*-**2x**	95[d]
4-MeOPh	4-MePh	*α*-**2y**	98[f]

[a] Typical reaction conditions: a mixture of benzil **1** (1 mmol) and NaI (5 mmol) was stirred in CH_2Cl_2 for 5 min. Then, 5 mmol of TMSCl was added to the solution, 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.

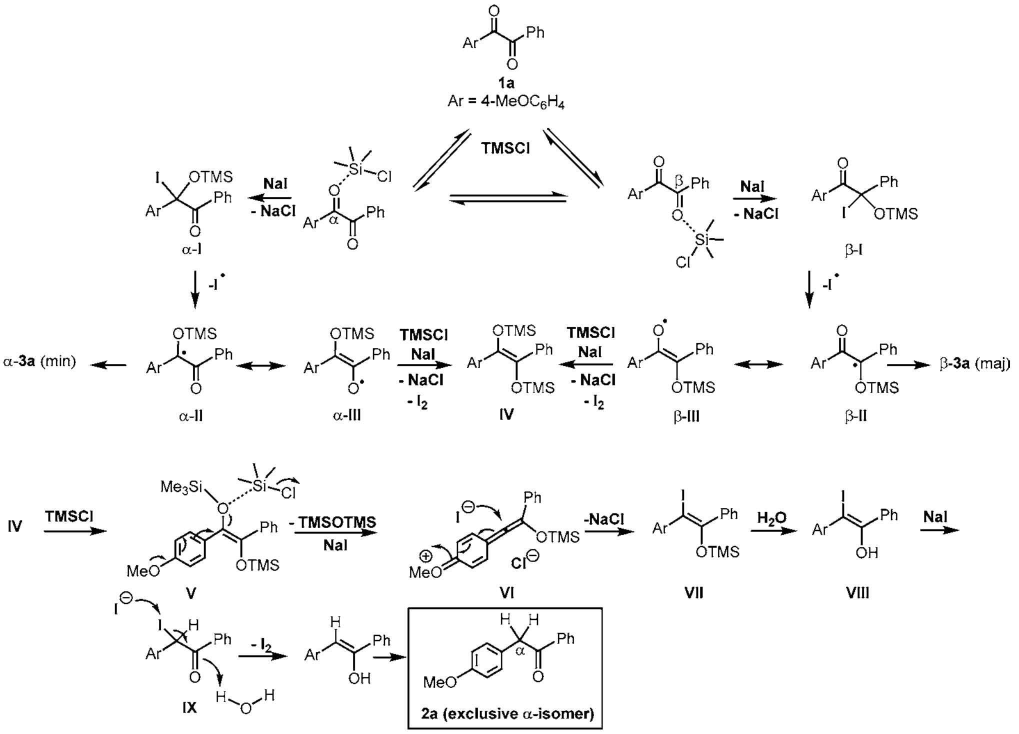
In all cases, and to our surprise, the reduction of these benzils proceeded overwhelmingly on the C*β* of diketones studied to furnish mainly *β*-benzoins **3a** and **3b** and exclusively *β*-**3x** with good to excellent yields.[12]

Scheme 2. Synthesis of DOBs 2 via Their Benzoin Intermediates 3



[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.

Scheme 3. Plausible Mechanism for the Regioselective Reduction of Benzil 1a into DOB α-2a Using TMSCl/NaI Combination in CH_2Cl_2

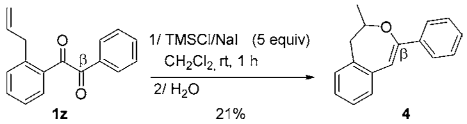


One can note that a less marked β-regioselectivity has been previously reported with very few examples of unsymmetrical benzils using other reducing agents such as alkylphosphines,[13] baker's yeast,[14] and NADH models.[15] Next, the reduction of benzoins **3a**,**b** and β-**3x** was attempted under 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-DOB regioisomers.

We next studied the spectroscopic data of the TMSCl/NaI combination via ^{1}H and ^{13}C NMR in CD_2Cl_2. Under argon, a solution of equimolar proportions of NaI and TMSCl in CD_2Cl_2 furnished a colorless solution with absorptions at δ ^{1}H 0.37 ppm and δ ^{13}C 1.34 ppm, rigorously identical with those of TMSCl alone (see Figure 1 in the Supporting Information). On the contrary, TMSI in CD_2Cl_2 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 TMSCl with NaI, in agreement with Olah's report.[1b]

To explain this unusual regioselective reduction of benzils **1** by the TMSCl/NaI combination in CH_2Cl_2, a plausible radical mechanism is proposed in Scheme 3. The reductive process begins probably by a coordination between oxygen atoms of **1a** with TMSCl followed by a nucleophilic 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 types α-**II** and β-**II** or their mesomeric forms α-**III** and β-**III**. Further reaction of **III** in the presence of TMSCl and NaI would furnish the intermediate **IV** and I_2, which colored the methylene chloride solution in brown.[16] Next, an additional equivalent of TMSCl would coordinate on the oxygen atom proximal to the electron-rich ring. The resulting intermediate **V** can lose TMSOTMS[17] with the help of the MeO substituent to furnish species **VI**, thus explaining the regioselectivity of this reducing process. All of our attempts to isolate TMSOTMS were unsuccessful; however, when Ph_3SiCl was used instead of TMSCl, $Ph_3SiOSiPh_3$ was successfully isolated after hydrolysis, reinforcing our ideas on this mechanism. A subsequent iodide atom addition on **VI** would give the alkenyl intermediate **VII**. After hydrolysis, the resulting enol **VIII** would react with NaI to provide α-iodoketone **IX**, which was reduced to **2a** by an iodide.[1b,18] To support this mechanistic hypothesis, incorporation of deuterium atoms into **2a** in separate experiments was tried. No D_2-labeled **2a** was observed when CD_2Cl_2 or TMSCl-d_9 was used. On the contrary, when **1a** was reacted with TMSCl/NaI in CH_2Cl_2, hydrolysis with D_2O 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,[19] **1z** having an *o*-allyl substituent, in which the terminal olefin would trap radical species, was reacted with TMSCl/NaI in CH_2Cl_2 (Scheme 4). Accordingly, a cyclized product **4** was isolated after hydrolysis in 21% yield, together with unidentified byproducts. This result strongly supports the radical mechanism[20] depicted in Scheme 3.

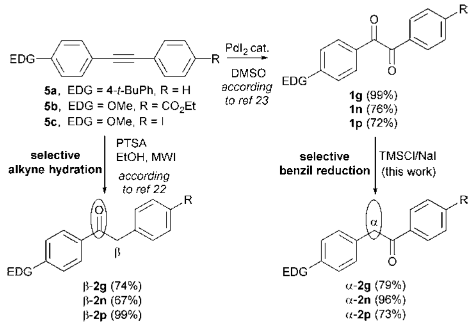
Scheme 4. Reaction of 1z with TMSCl/NaI Combination in CH_2Cl_2 at rt



Because deoxybenzoins are important structural moieties that occur in bioactive molecules,[21] 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 DMSO[23] in the presence of catalytic amounts of PdI_2. 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.

Scheme 5. Regioselective Access to *α*-DOBs 2g, 2n, or 2p or *β*-DOBs 2g, 2n, or 2p from Diarylalkynes 5a−c



In summary, we have demonstrated for the first time that the TMSCl/NaI combination in CH_2Cl_2 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 for 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 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01491.

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

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Notes

The authors declare no competing financial interest.

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(9) Identification of *α*-**2a** was determined by COSY, NOESY, HMBC, and HSQC experiments.

(10) When **1a** was treated with HI (wt 57%) in refluxing AcOH according to Fuson's conditions (ref 8b), **2h** was obtained (80%) indicating that a demethylation occurred to provide a phenolic species.

(11) ^1H NMR results revealed that the crude consists of a mixture of *α*-**2a**/*β*-**3a**/*α*-**2h** in a 15/75/10 ratio.

(12) Identification and ratio of regioisomers *α*-**3a**/*β*-**3a** was determined by COSY, NOESY, HMBC and HSQC experiments on the crude mixture.

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(19) Addition in the media of 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 **1z** into **4**, we discarded the formation of intermediate **IV** through a reaction of *α*-I or *β*-I with an iodine atom.

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