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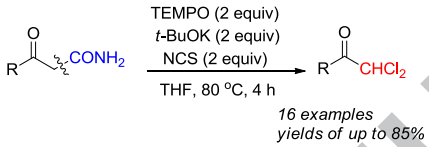

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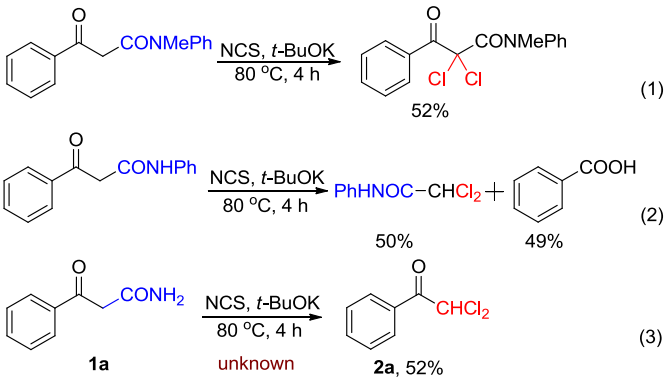
ABSTRACT

An approach to the dichlorinative deamidation of primary β-ketoamides through ketonic cleavage is described, and a series of α,α-dichloroketones were furnished mostly in the presence of TEMPO. Based on control experiments, a mechanism involving tandem dichlorination and deamidation is proposed to interpret the observed reactivity.

1. Introduction

In the practice of organic chemistry, both the elongation and shortening of carbon chains possess identical importance. Amides are a significant functional group[1] and capable of being transformed by hydrolyzing the cyano group[2] or oxidizing the α-carbon of the amino group[3]. Amides can be further derivatized to important functional groups such as carboxylic acids, esters, acyl halides and oxazoles[4], all of which have been extensively applied in the synthesis of pharmaceuticals, natural products and important organic polymers. A one-step strategy to disconnect the C−C bond of amides is reportedly feasible, and hence amides can be further derived into other functional groups as required.[5] However, not all amides groups can be readily removed or degraded, and, apart from the reaction conditions, the structure of the amide appears to have an extremely important influence on deamidation.

Halogenation[6] and pseudohalogenation[7] are significant chemical transformations in organic synthesis, because they are capable of easily converting into other functional molecules.[8] Dichlorination on tertiary and secondary β-ketoamides has been investigated.[9] According to the reported procedure[9c,9f] in our tentative work, the tertiary amide N-methyl-3-oxo-N,3-diphenylpropanamide only yielded the 2,2-dichlorosubstituted product 2,2-dichloro-N-methyl-3-oxo-N,3-diphenylpropanamide without C-C bond cleavage in 52% yield (eq. 1, Scheme 1), and the secondary amide 3-oxo-N,3-diphenylpropanamide led to 2,2-dichloro-N-phenylacetamide in 50% yield, accompanied by benzoic acid in an isolated yield of 49% after acidification, which demonstrates acidic cleavage (eq. 2). Different from secondary β-ketoamides, when the corresponding primary 3-oxo-3-phenylpropanamide **1a** was employed (eq. 3), ketonic cleavage occurred, in which two H atoms on the nitrogen were requisite for the deamidation process and 2,2-dichloroacetophenone **2a** was obtained in 52% yield. To the best of our knowledge, the dichlorinative deamidation of β-ketoamides has not been developed using primary amides as substrates to date. Therefore, we report the successful dichlorinative deamidation of primary β-ketoamides through ketonic cleavage in one pot.



Scheme 1. Influence of N-substitution on the dichlorination of β-ketoamides.

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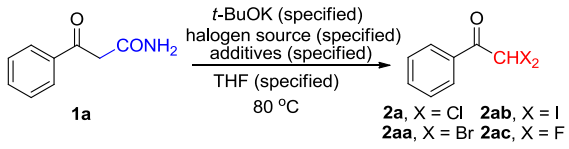
2. Results and discussion

Initially, we investigated dichlorinative deamidation using 3-oxo-3-phenyl-propanamide (**1a**) as the model substrate. In the presence of 1.8 equivalents of N-chlorosuccinimide (NCS) and 2.0 equivalents of *t*-BuOK in tetrahydrofuran (THF) at 80 °C for 4 h, the corresponding 2,2-dichloroacetophenone **2a** was generated in an isolated yield of 52% (Table 1, entry 1). A variety of bases, solvents, reaction temperatures and oxidants were examined to determine the optimal reaction conditions for the deamidative transformation (for details, see the Supporting Information). Various bases such as K_2CO_3, *t*-BuONa, KOH, K_3PO_4 and CH_3ONa gave lower yields than *t*-BuOK. CsF afforded only a small amount of the chlorinated product. Various solvents were also screened. Consequently, ether solvents including diethyl ether, butyl ether, dioxane, anisole and 2-methyltetrahydrofuran, haloalkane solvent dichloromethane and chloroform, aromatic solvent toluene, acetonitrile and DMSO led to inferior results, compared with THF yielding the dichlorinated product in 52%. Ester solvents such as ethyl acetate, alcohol solvents such as methanol, and DMF failed to promote the reaction. This transformation also proved to be temperature-sensitive, and as a result either lowering or raising the reaction temperature greatly decreased the yields. When other halogenation reagents such as NBS, NIS and F-TEDA were examined for dibromination, diiodination and difluorination, respectively, only NBS was compatible with the reaction conditions, and 2,2-dibromo-1-phenylethanone (**2aa**) was isolated in 28% yield (entries 2-4).

To further optimize the reaction conditions, other parameters were sequentially investigated. Neither decreasing nor increasing the amount of *t*-BuOK improved the efficiency of dichlorinative deamination (entries 5-7). Notably, 2-chlorosubstituted amide **3** was obtained in 44% yield and was not accompanied by a deamination product without the addition of *t*-BuOK to the reaction system, which indicates that basic conditions are essential to deamination (entry 6). To our delight, the yield of this transformation was improved to 70% when an additional 1 mL of THF was injected to dissolve as much of the low-solubility β-ketoamides (**1a**) as possible (entry 8). Three milliliters of THF did not accelerate the reaction efficiency due to the lower reaction concentration (entry 9). The addition of 2 equivalents of NCS reasonably improved the yield to 79% (entry 10). A slight decrease in conversion was observed when 2.2 equivalents of NCS was added (entry 11). Neither extending nor shortening the reaction time was beneficial to the yield (entries 12 and 13). By contrast, under argon protection in dry THF, the reaction had a yield of 78%, which was similar to the unprotected reaction (entry 14). We then investigated the additive influence on deamidative transformation (for details, see the Supporting Information). As a result, only 2.0 equivalents of TEMPO increased the yield to 83% (entry 15), whereas a catalytic amount of TEMPO resulted in a lower yield. Accordingly, the optimal conditions were identified as 2.0 equivalents of NCS reacting with 3-oxo-3-phenyl-propanamide in THF in the presence of 2.0 equivalents of *t*-BuOK and TEMPO at 80 °C for 4 hours.

Table 1. Optimization of the reaction conditions[a]

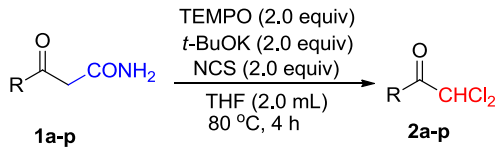


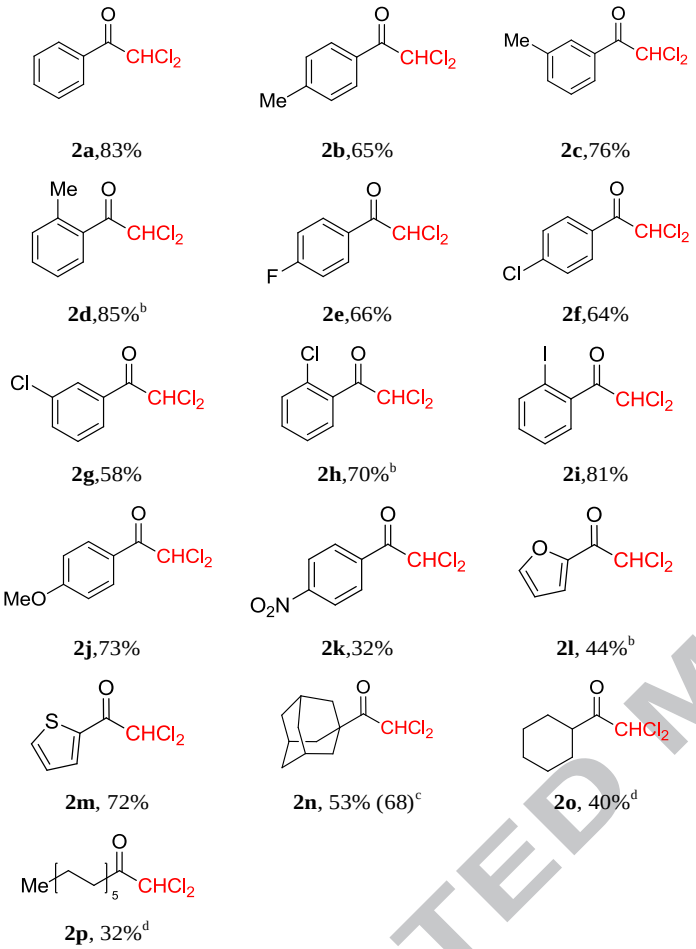
Entry	*t*-BuOK (eq.)	THF (mL)	Halogen sources	Yield[b] (%)
1	2.0	1.0	1.8 equivalents of NCS	52
2	2.0	1.0	1.8 equivalents of NBS	28
3	2.0	1.0	1.8 equivalents of NIS	n.r.[c]
4	2.0	1.0	1.8 equivalents of F-TEDA	n.r.
5	1.8	1.0	1.8 equivalents of NCS	40
6	0	1.0	1.8 equivalents of NCS	0 (44)[d]
7	2.2	1.0	1.8 equivalents of NCS	50
8	2.0	2.0	1.8 equivalents of NCS	70
9	2.0	3.0	1.8 equivalents of NCS	54
10	2.0	2.0	2.0 equivalents of NCS	79
11	2.0	2.0	2.2 equivalents of NCS	75
12	2.0	2.0	2.0 equivalents of NCS	55[e]
13	2.0	2.0	2.0 equivalents of NCS	70[f]
14	2.0	2.0	2.0 equivalents of NCS	78[g]
15	2.0	2.0	2.0 equivalents of NCS	83[h]

[a]Reaction conditions: **1a** (0.5 mmol), NCS (specified) and *t*-BuOK (specified) in THF (specified) at 80 °C for 4 h. [b]Isolated yields. [c]n.r. = no reaction. [d]Isolated yield of 2-chloro-3-oxo-3-phenylpropanamide **3**. [e]3 h. [f]5 h. [g]Dry THF under Ar. [h]2.0 equivalents of TEMPO. NCS = N-chlorosuccinimide, NBS = N-bromosuccinimide, NIS = N-iodosuccinimide, F-TEDA = Selectfluor.

Using the optimal reaction conditions, we explored the functional group tolerance of dichlorinative deamidation. Firstly, the model substrate showed favorable reactivity in this reaction (**2a**). *para*-, *meta*-, and *ortho*-Substituted aromatic, heterocyclic or aliphatic 3-oxo-propanamide were all suitable for this transformation and furnished the standard diverse α,α-dichlorinated ketones in moderate to good yields. A variety of mono-methyl-substituted model substrates performed with good chemical reactivity (**2b-d**). As another example, β-ketoamides bearing halide substituents such as F, Cl and I were also tolerated in this conversion, and moderate to good reactivities were observed (**2e-i**). Notably, not only methyl substituents but also halide substituents at the *ortho*-position of the aromatic ring showed higher reactivity in this deamidative ketonic cleavage reaction (**2d**, **2h** and **2i**) than their *meta*- and *para*-substituents, which rationally suggests that the congested structure is readily degraded to smaller molecules of dichloroketone based on the low-energy preference. The electron-donating methoxy group at the para-position of the aromatic ring had a dominant advantage over the electron-withdrawing nitro group (**2j-k**). Furthermore, the reaction conditions were also suitable for the deamidation of heterocyclic β-ketoamides such as furan and thiophene rings, affording the corresponding ketones in 44% and 72% yields, respectively (**2l-m**). Aliphatic β-ketoamide **1n** was also investigated in this reaction, and **2n** was obtained in a modest yield of 53%. However, in the presence of a catalytic amount of TEMPO, dichloroketone **2n** was obtained in a credible yield of 68%, which is in stark contrast to the previously evaluated conditions (see the Supporting Information). Likewise, several other β-ketoamides such as **1e**, **1f**, and **1m** were examined in a catalytic amount of TEMPO, but their yields failed to improve (for details, see the Supporting Information). Aliphatic β-ketoamides with both sides of the β-carbonyl bearing α-hydrogen atoms were also investigated under the standard conditions, and amides **1o** and **1p** led to difficult-to-purify products (**2o-p**) in modest yields of 40% and 32%, respectively, which were determined by ^{1}H NMR spectroscopy. Consequently, we attempted to adjust the reaction conditions to isolate the dichlorinative deamidation product in the following work.

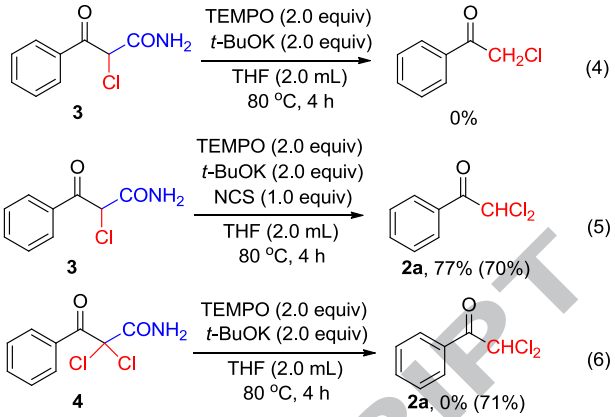
Table 2. Substrate scope[a]





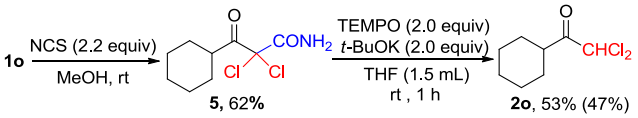
[a]Isolated yields. [b]Yields without TEMPO. [c]0.2 equivalents of TEMPO. [d]Yields of **2** determined by ^{1}H NMR spectroscopy using 1,3,5-trimethylbenzene as the internal standard.

To gain insight into this transformation, several control experiments for the deamidation of α-chlorinated and α,α-dichlorinated β-ketoamides were conducted. Without addition of NCS, the deamidation of amide **3** to obtain an α-chloroketone did not proceed (eq. 4, Scheme 2). When 1.0 equivalent of NCS was added under the adjusted reaction conditions, the deamidation product **2a** was generated in 77% yield (eq. 5). α,α-Dichlorinated β-ketoamide **4** directly underwent deamidation to provide **2a** in 71% yield, but the deamidation process failed to proceed with the addition of 2.0 equivalents of TEMPO (eq. 6). Thus, we speculate that this deamidative transformation goes through dichlorination and deamidation reactions. In the presence of TEMPO, amide **4** did not yield product **2a**, which indicates that TEMPO facilitates the dichlorination and is detrimental to the second step, i.e., deamidation.



Scheme 2. Control experiments. Yields without TEMPO in parentheses.

A two-step synthetic method of dichlorinative deamidation was explored, employing the pre-prepared α,α-dichlorinated β-ketoamide **5** as the substrate under the optimal reaction conditions. The desired product **2o** was successfully synthesized in 53% isolated yield (Scheme 3). In this process, TEMPO did not have negative effects on deamidation, presumably due to the existence of the α-H of the carbonyl group. The α-H is involved in the enolization in the presence of *t*-BuOK and then generates the enolate. Through intramolecular S_N2 substitution, the α-chlorine of the enolate results in the formation of the cyclopropanone amide, which proceeds in the deamidation reaction to generate α-chlorocyclopropanone. The ring opening of the cyclopropanone occurs through nucleophilic attack of the chlorine anion in the presence of *t*-BuOH and eventually reaches the α,α-dichloroketone **2o** (see the Supporting Information).



Scheme 3. Deamidation of 2,2-dichlorinated aliphatic β-ketoamide **5**. Yield without TEMPO in parentheses.

In summary, we developed a novel approach for the dichlorinative deamidation of primary β-ketoamides through ketonic cleavage in one pot. Most β-ketoamides furnished a series of α,α-dichloroketones in moderate to good yields in the presence of TEMPO. Based on the control experiments, a mechanism was proposed involving tandem dichlorination and deamidation.

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Supplementary Material

Supplementary data (detailed experimental description and condition optimization; characterization data of NMR for all compounds; details of copies of the 1H NMR and 13C NMR) associated with this article can be found in the online version.

Research highlights

► An approach for the dichlorinative deamidation of primary β-ketoamides is developed. ► Primary β-ketoamide gaves rise to dichlorinated ketone through a ketonic cleavage. ► A mechanism involving tandem process of dichlorination and deamidation is proposed.