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Approach for the Direct Synthesis of *β*-Dichlorosubstituted Acetanilides Using Iodine Trichloride (ICl_3) as the Oxidant and Catalyst

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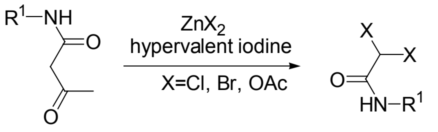
A reliable method for direct synthesis of *β*-dichlorosubstituted acetanilides is reported. The key transformation involves the oxidative and catalytic cleavage of a carbon-carbon bond in the presence of iodine trichloride (ICl_3). In this protocol ICl_3 is used not only as the catalyst but also as the oxidant which widely broadens the scope of its application in organic synthetic chemistry.

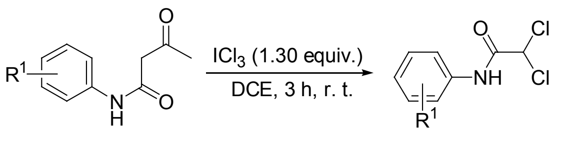
Keywords iodine trichloride (ICl_3), cleavage of carbon-carbon bond, 3-oxo-*N*-phenylbutanamides, *β*-dichlorosubstituted acetanilides

Introduction

Our group has great interest in the fields of cleavage or construction of C—C and C-hetero bond using hypervalent iodine reagents as oxidant or (and) catalyst (Eq. 1).[1-8] This paper reports a new approach for direct synthesis of *β*-dichlorosubstituted acetanilides in the presence of iodine trichloride (ICl_3). Nowadays, hypervalent iodine reagents, as oxidants, have received much attention due to their low toxicity, mild reactivity, ready availability, high stability, easy handling, *etc*.[9-20] Herein, the ICl_3 in this work was used not as the oxidant but also as the catalyst (Eq. 2).



(1)

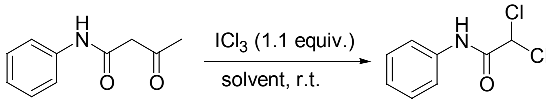


(2)

Experimental

Initially, we tried to establish an effective reaction system based on the above-mentioned transformation. A brief optimization about the reaction solvent, amount of ICl_3 and time on the model reaction was carried out. The results are summarized in Table 1. The model reaction of 3-oxo-*N*-phenylbutanamide **1a** in dioxane at room temperature occurred in the presence of iodine trichloride (ICl_3). After the screening of reaction time, we found that 3 h was the optimal reaction time for the completion of this transformation (Entries 1—3). Among the various solvents examined, 1,2-dichloroethane (DCE)

Table 1 Optimization of reaction conditions[a]



1a **2a**

Entry	Solvent	Reaction time/h	Yield[b]/%
1	Dioxane	1	30
2	Dioxane	3	48
3	Dioxane	5	49
4	Cyclohexane	3	37
5	CH_2Cl_2	3	88
6	DCE	3	91
7	DMF	3	35
8	DMSO	3	21
9[c]	DCE	3	96
10[d]	DCE	3	96

[a] The reaction was carried out using 0.25 mmol of **1a**, 1.10 equiv. of ICl_3, 2.0 mL of solvent; [b] GC yield; [c] 1.30 equiv. of ICl_3; [d] 1.50 equiv. of ICl_3.

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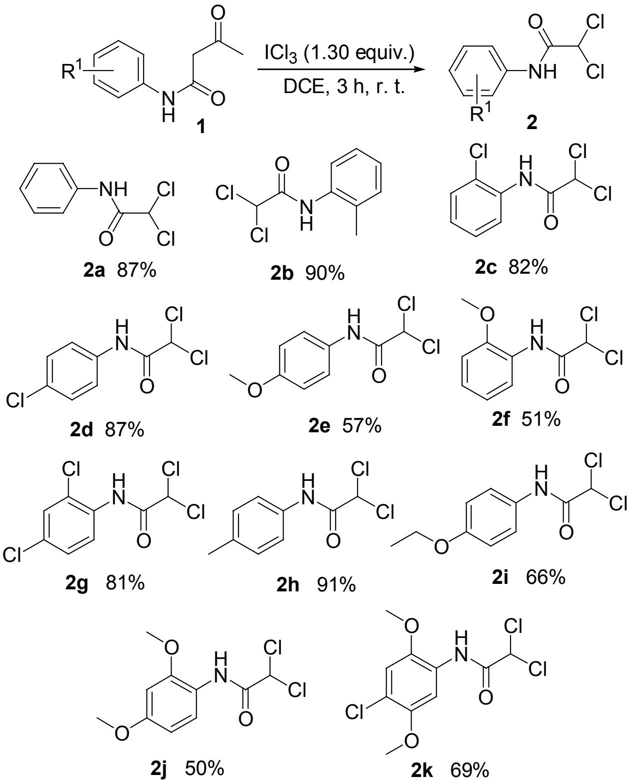
was more efficient for the explored reaction than others (Entries 4—8) and resulted in the desired product in 91% GC yield (Entry 6). It is noteworthy that this transformation appears quite sensitive to the solvent. For example, the reaction resulted in an obvious decrease of the yield in *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) (Entries 7 and 8). Finally, we investigated the effect of the amount of iodine trichloride on the reaction (Entries 9 and 10), the result indicated that 1.3 equivalent of ICl_3 was sufficient for the completion of this reaction (Entry 9).

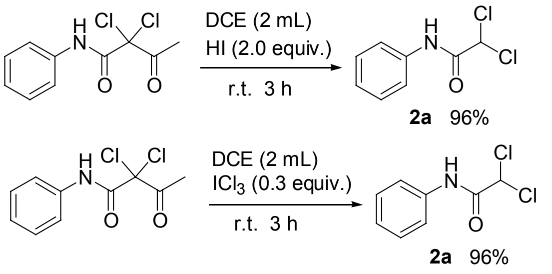
Next, we conducted a survey of the reaction scope. As shown by the results compiled in Scheme 1, a range of reactions were performed with various *β*-ketobutylanilides **1**. It was observed that all reactions appeare quite sensitive to electronic contribution of substituted groups on benzene ring of *β*-ketobutylanilides, the substrates, such as **1e**, **1f**, **1i** and **1j**, with strong electron-donating substituted groups on benzene ring, all afforded the corresponding *β*-dichlorosubstituted acetanilide **2e**, **2f**, **2i** and **2j** with lower isolated yield comparing to the substrates with weak electron-withdrawing or weak electron-donating groups, such as chloro- and methyl, on benzene ring (**1a**—**1d**).

Scheme 1 The synthesis of dichloroacetamides (Notes: All the reactions were carried out with **1** (1.0 mmol), DCE (2 mL), ICl_3 (1.30 equiv.); All the listed yields were isolated yield.)



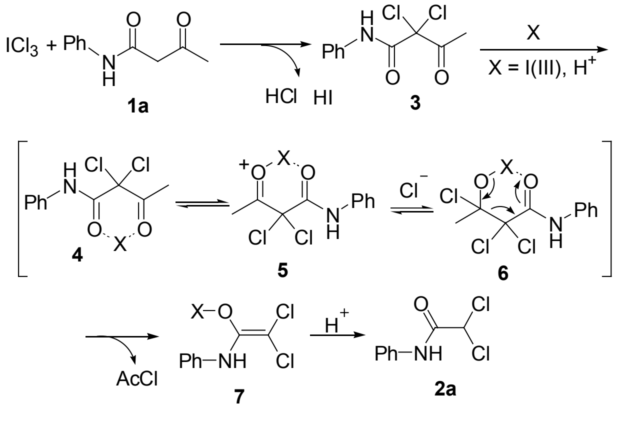
To probe the mechanism of this transformation, we ran two control experiments (Scheme 2). Interestingly, we were pleased to find that the reaction proceeded smoothly and almost gave the quantitative product **2a** under the two reaction conditions. Also, we investigated the reaction rates of the two reactions, we found that the two reactions both need 3 h to complete the reaction, but the sufficient amount to catalyze the reaction was different. HI needed 2.0 equiv., while ICl_3 only needed 0.3 equiv., to complete the reaction in 3 h.

Scheme 2 Probe the mechanis



On the basis of these preliminary results, a hypothetic reaction pathway was listed in Scheme 3, exemplified by the formation of **2a**. The first step involves the dichlorination of the *β*-keto amide of 3-oxo-*N*-phenylbutanamide (**1a**) to give intermediate **3** and the release of HCl and HI. It is well known that iodide and Brønsted acid are often used as the activating agent in organic synthetic chemistry to activate the electron-deficient functional groups,[21-26] such as, carbonyl group.[27] Therefore, the coordination of the carbonyl to the X (X=I(III) and H^+) generates intermediate **4**, and **5**. The nucleophilic attacks of chloridion on the carbonyl carbon of **5** and results in intermediate **6**. The following carbon-carbon bond cleavage of the labile *α*,*α*-dichloro-*β*-keto amide **6**[28] generates intermediate **7** by elimination one equivalent of AcCl. Finally, under the acid conditions, through an isomerization process, the final product 2,2-dichloroacetanilide (**2a**) was produced from the intermediate **7**.

Scheme 3 Tentative mechanism for the synthesis of 2,2-dihalo-*N*-phenylacetamides



Conclusions

In summary, we have shown an efficient and operationally simple method to synthesize *β*-dichlorosubstituted acetanilides. Nowadays, due to the favorable characteristics, such as safety, mildness, and environmental friendiness of hypervalent iodine reagents, they are widely utilized in synthetic processes as oxidant. This work successfully realized the duel role of ICl_3 as the oxidant and catalyst. The current direction for future research is aimed at extending the scope and potential synthesis applications.

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