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Zwitterion-Catalyzed Deacylative Dihalogenation of β-Oxo Amides

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02701 Read Online

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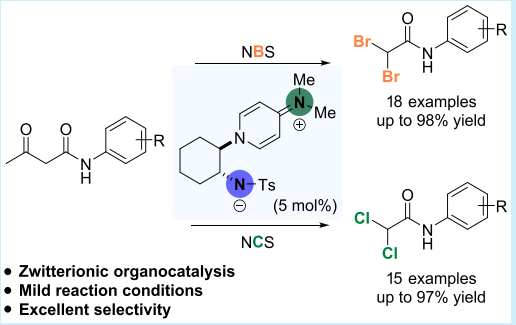
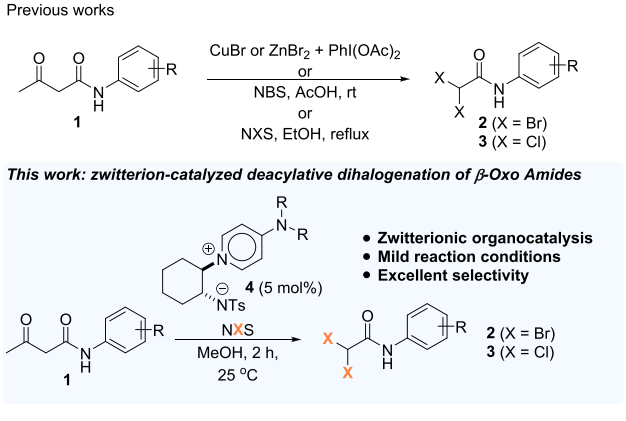
ABSTRACT: α,α-Dihalo-*N*-arylacetamides are commonly used as intermediates in various organic reactions. In the study described here, a catalytic synthesis of α,α-dihalo-*N*-arylacetamides from β-oxo amides was developed using zwitterionic catalysts and *N*-halosuccinimides as the halogen sources. The corresponding α,α-dihalo-*N*-arylacetamides were obtained in good to excellent yields, and no aromatic halogenated side products were detected. The reaction conditions were mild, and no strong base or acid was required.



The deacylative halogenation of β-oxo amides is a useful reaction because the α,α-dihaloamide products are the constitutional elements of many biologically active compounds, for example, the antibiotic drugs florfenicol[1] and chloramphenicol.[2] In addition, the halogens in α,α-dihaloamides can be readily manipulated to give various functional groups such as hydrazine[3] and thiourea.[4] Applications of α,α-dihaloamide compounds as organocatalysts[5] and herbicide antidotes[6] have also been reported. This type of molecule cannot be prepared simply by the direct halogenation of acetamides because overhalogenation to trihalogenated compounds readily occurs.[7] Hence the development of efficient methods to synthesize versatile α,α-dihaloamide intermediates is of great importance for both industrial and academic sectors.[8]

In recent years, a number of methods for the synthesis of α,α-dihaloamides **2** and **3** via the deacylative dihalogenation of β-oxo amides **1** have been documented.[9] For example, using *N*-bromosuccinimide (NBS) with acetic acid (at room temperature) or ethanol (under reflux) was also found to be viable.[9a,c] Using CuBr or $ZnBr_2$ as the bromine source together with $PhI(OAc)_2$ as the oxidant was also documented.[9d] However, these reactions involve the use of a stoichiometric amount of metal salt, acidic media, or high temperature, which is undesirable. Zwitterionic catalysts, which involve site isolation of the positively and negatively charged partners in the same molecules while the overall charge is neutral,[10] have been applied in some important chemical reactions under mild conditions.[11,12] Our group also reported the use of zwitterions to catalyze some chemical transformations.[13] For instance, zwitterion **4** was found to be highly active in catalyzing the transesterification of alcohols.[13c] Herein we describe a novel and efficient synthesis of α,α-dihaloarylamides **2** and **3** from β-oxo arylamides **1** using zwitterionic catalyst **4** and the inexpensive and easy-to-handle *N*-halosuccinimide as the stoichiometric halogen source under mild conditions (Scheme 1).

Scheme 1. Deacylative Dihalogenation

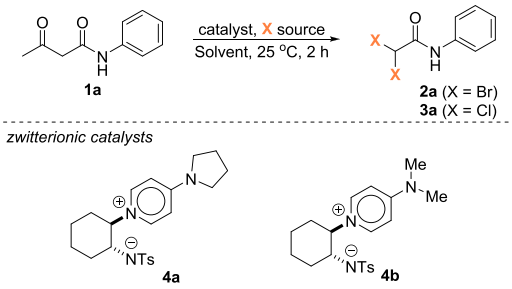


At the beginning of the investigation, acetoacetanilide (**1a**) and NBS were used as the substrate and the halogen source, respectively (Table 1). The background reaction was found to be sluggish (entry 1). A significant amount of aromatic bromination side product was detected when EtOH was used as the solvent (entry 2). The desired product **2a** was obtained

Received: August 13, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02701
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Conditions Optimization[a]



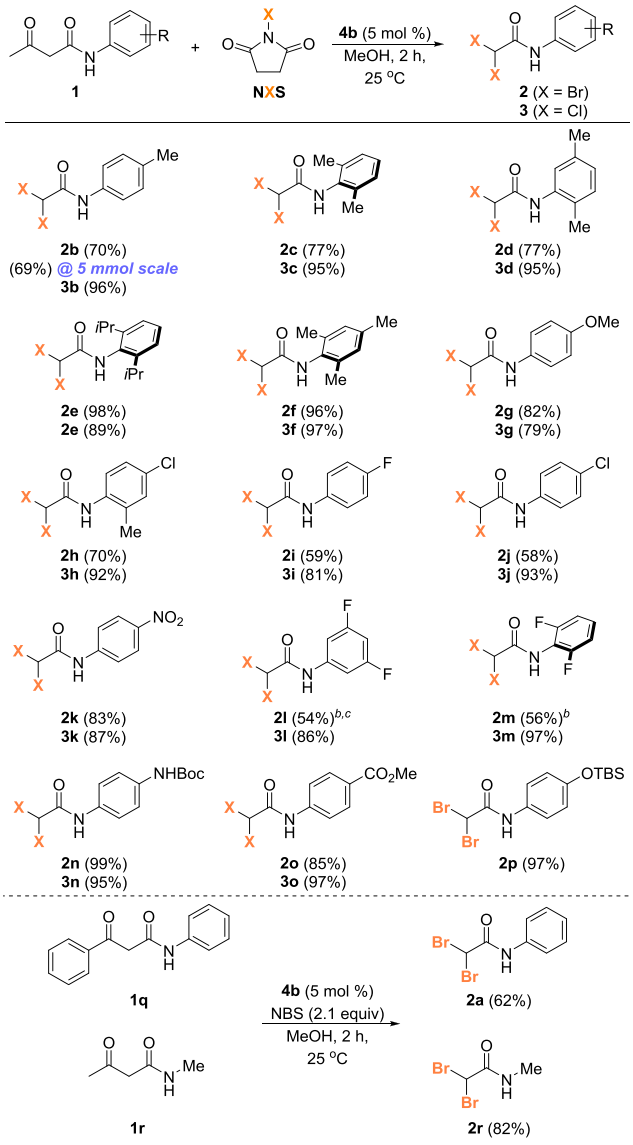
entry	Br source	cat. (mol %)	solvent	yield (%)
1	NBS	none	MeOH	9
2	NBS	none	EtOH	0[c]
3[b]	NBS	NaOMe (20)	MeOH	28
4[b]	NBS	K_2CO_3 (20)	MeOH	28
5[b]	NBS	DABCO (20)	MeOH	37
6[b]	NBS	DMAP (20)	MeOH	49
7[b]	NBS	**4a** (20)	MeOH	76
8[b]	NBS	**4b** (20)	MeOH	97
9	NBS	LiNMeTs (20)	MeOH	21
10	NBS	*N*-Methylpyridinium iodide (20)	MeOH	trace
11	NBS	**4b** (10)	MeOH	93
12	**NBS**	**4b (5)**	**MeOH**	**89**
13	NBS	**4b** (5)	CH_2Cl_2	trace
14	NBS	**4b** (5)	$CHCl_3$	trace
15	NBS	**4b** (5)	PhMe	trace
16	NBA	**4b** (5)	MeOH	70
17	NBP	**4b** (5)	MeOH	trace
18	NCS	**4b** (5)	MeOH	90

[a]Reactions were carried out with **1a** (0.05 mmol), a Br source (0.105 mmol), and a catalyst in solvent (1 mL) at 25 °C in the absence of light for 2 h. The yields were measured using NMR with nitromethane as the internal standard. [b]Reaction time was 30 min. [c]11% of aromatic brominated products was observed. DABCO, 1,4-diazabicyclo[2.2.2]octane; DMAP, 4-dimethylaminopyridine.

in low yield when alkali metal bases (NaOMe, K_2CO_3) or amine bases (DABCO, DMAP) were used as the promoters (entries 3−6). To our delight, zwitterionic catalyst **4a** (20 mol %) effectively promoted the reaction to give **2a** in good yield (76%) with no aromatic bromination (entry 7). The reaction efficiency was further enhanced when zwitterion **4b** was used as the catalyst (entry 8). LiNMeTs and *N*-methylpyridinium iodide were found to be inefficient in catalyzing the reaction (entries 9 and 10), suggesting that the anionic and cationic parts of **4b** might work synergistically. A comparable yield was obtained even when the catalyst loading was reduced to 5 mol % (entries 11 and 12). Other reaction media such as dichloromethane, chloroform, and toluene were found to be not suitable (entries 13−15). The performance of NBS was found to be superior to that of other brominating agents such as *N*-bromoacetamide (NBA) and *N*-bromophthalimide (NBP) (entries 16 and 17). α,α-Dichloroarylamide **3a** was obtained when *N*-chlorosuccinimide (NCS) was used as the halogen source (entry 18).

After the optimization of reaction conditions, the substrate scope of the deacylative dibromination reaction was evaluated (Scheme 2). For substrates **1b−g** with electron-donating substituents (alkyl and methoxy groups) on the phenyl ring, the reaction smoothly proceeded to give the products **2b−2g** in good to excellent yields. The reaction was readily scalable

Scheme 2. Scope of the Deacylative Dihalogenation[a]



[a]Reactions were carried out with **1** (0.30 mmol), NBS (for product **2**) or NCS (for product **3**) (0.63 mmol), and **4b** (0.015 mmol) in MeOH (6 mL) at 25 °C in the absence of light for 2 h. The yields were isolated yields. [b]10 mol % of **4b** was used, and ca. 40% of the starting material was recovered. [c]Trace amount of product was detected when the reaction was conducted at 75 °C in EtOH for 12 h in the absence of catalyst.

(5.0 mmol of **1b**), and the desired product **2b** was obtained in comparable yield. The catalytic protocol was also found to be compatible with substrates **1h−k** bearing electron-withdrawing substituents to give **2h−k**. For the highly electron-deficient difluorinated substrates **1l** and **1m**, the reactions were operated using 10 mol % of zwitterionic catalyst **4b**. Functional groups including NBoc, ester, and silyl ether were also compatible with the catalytic protocol, giving **2n−p** in good yields. β-Oxo amide **1q** bearing the benzoyl substituent was successfully dibrominated and deacylated, giving **2a** in 62% yield. The *N*-alkylated substrate **1r** worked well in the reaction to give **2r** in 82% yield. After studying the deacylative dibromination, we turned our attention to the synthesis of α,α-dichloroarylamides using NCS as the halogen source. To our delight, excellent

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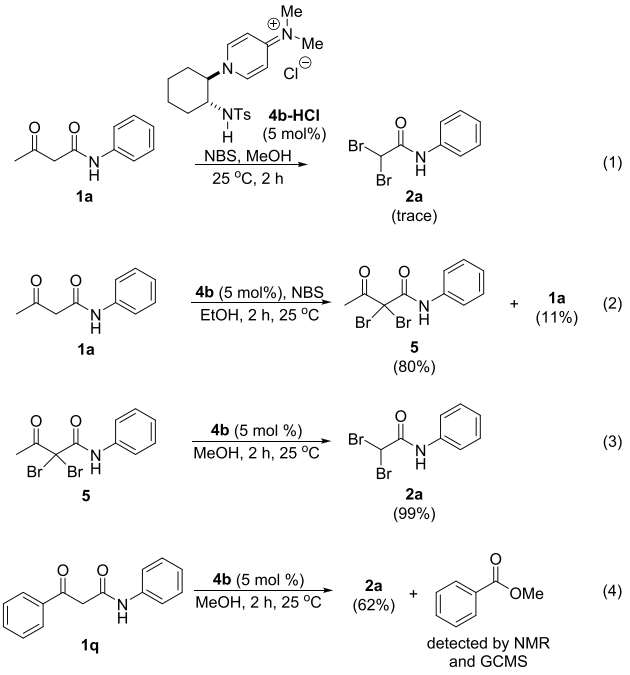
yields of the desired products (**3b**−**o**) were obtained for substrates bearing electron-donating or electron-withdrawing substituents.

Some control experiments were conducted to shed light on the mechanistic picture. Zwitterion **4b** was acidified with 1 equiv of HCl (i.e., **4b-HCl**) before being added to the reaction mixture (Scheme 3, eq 1). Only a trace amount of the desired

Scheme 3. Control Experiments



product **2a** was detected, revealing the importance of the basic amide of **4b** in the catalysis. In literature, 2,2-dibromo-*N*-phenyl-3-oxo-butanamide **5** is believed to be the key intermediate for the deacylative dihalogenation reaction of *β*-oxo amide.[9] Indeed, a small amount of **5** was detected during the reaction in MeOH, and it eventually diminished. When using EtOH as the solvent, the reaction was relatively slow, and a sufficient amount of **5** was isolated (Scheme 3, eq 2). When **5** was used as the substrate, **2a** was obtained quantitatively, suggesting that **5** might be an intermediate in the reaction (Scheme 3, eq 3). For the reaction with **1q**, methyl benzoate was detected after the reaction, revealing the deacylation process by the alcohol (Scheme 3, eq 4).

NMR experiments were conducted to understand the interaction between *β*-oxo amide **1b** and zwitterion **4b** (Figure 1). Instead of CD_3OD, CD_2Cl_2 was employed in all three spectra as the NMR solvent to prevent the intervention of the protic solvent. In Figure 1A, the sharp singlet peak at δ 3.6 corresponds to the two *α*-carbonyl protons H^a in **1b**. The signal disappeared completely upon the addition of 1 equiv of **4b**, and a new board signal at δ 4.7 emerged (Figure 1C). Concurrently, the C−H bonds adjacent to the C−N bonds (H^b and H^c, Figure 1B) in zwitterion **4b** shifted downfield (Figure 1C). These observations could be attributed to the interaction between the basic amide in zwitterion **4b** and the acidic proton in **1b**.

On the basis of the aforementioned results and literature reports,[9,14] a plausible mechanistic picture of the deacylative dibromination of *β*-oxo amide is illustrated in Scheme 4. We

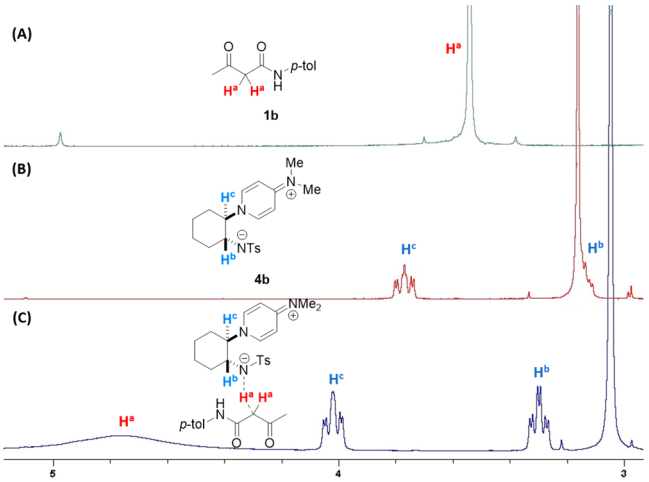
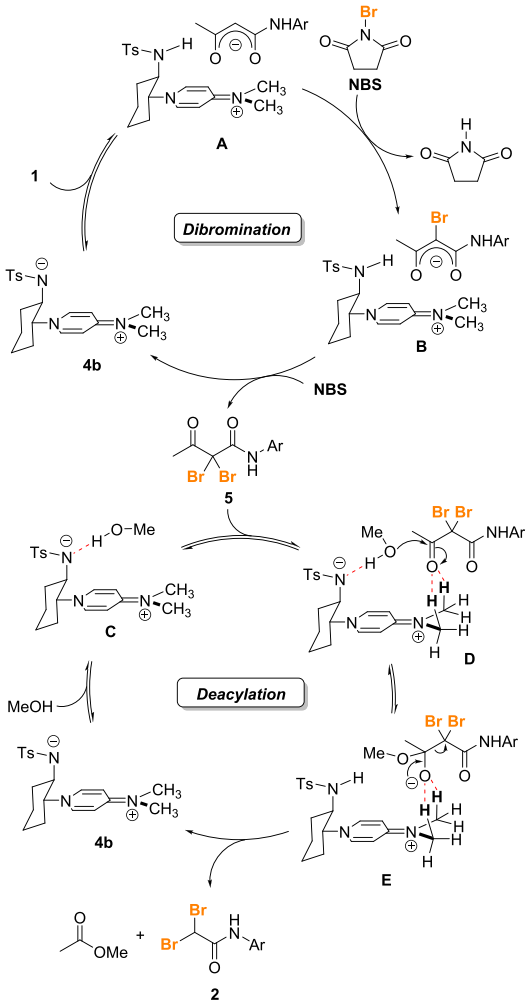


Figure 1. NMR experiments.

Scheme 4. Proposed Mechanism



speculate that the amide of zwitterion **4b** might deprotonate the *β*-oxo amide **1** to give the enolate species **A**. NBS might then react with species **A** to give the monobrominated species **B**, which could be further brominated to give dibromide **5**. On the basis of our previous study on the transesterification reactions, zwitterion **4b** is capable of deprotonating alcohols while the iminium cation stabilizes the carbonyl oxygen via a

https://dx.doi.org/10.1021/acs.orglett.0c02701
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nonclassical hydrogen bond interaction.[13c] Thus we believe that zwitterion **4b** might react with methanol to give methoxide species **C**. The carbonyl oxygen of **5** might be activated by the iminium cation of species **C** to give species **D**. Subsequently, the methoxide might attack the carbonyl carbon to give species **E**. The process might be slow with the relatively bulkier EtOH, which might explain why a significant amount of **5** was detected for the reaction with EtOH (Scheme 3, eq 2). Finally, retro-Claisen condensation[15] by eliminating a molecule of methyl acetate could furnish the desired α,α-dibromoamide product **2** together with the regeneration of the zwitterionic catalyst **4b**. Thus, in this reaction, we believe that the zwitterion might have dual roles: (1) promoting the halogenation of β-oxo amides to α,α-dihalo-β-oxoamides and (2) the synergistic activation of MeOH and the carbonyl of α,α-dihalo-β-oxoamides in the deacylation process.

In summary, a mild, efficient deacylative dihalogenation of β-oxo amides has been developed. Instead of using a metal or strong acid/base, a novel and stable zwitterionic catalyst was employed in low catalyst loading. The reactions were operated under mild conditions with easy-to-handle *N*-halosuccinimides as the halogen sources.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02701.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the financial support from the Research Grants Council of the Hong Kong Special Administration Region (project no. CUHK14305520), The Chinese University of Hong Kong Direct Grant (project no. 4053394), and the Innovation and Technology Commission to the State Key Laboratory of Synthetic Chemistry (GHP/004/16GD).

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