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Authors: Lianghua Zou, Yanchun Li, Pinggui Li, Jing Zhou, and Zhimeng Wu

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Solvent-Controlled *α*-Monobromination, *α*,*α*-Dibromination or Imidationof 1,3-Diketones with *N*-Bromosuccinimide

Liang-Hua Zou,*[a] Yan-Chun Li,[a] Ping-Gui Li,[b] Jing Zhou,[a] and Zhimeng Wu*[a]

Abstract: In this work, we present a solvent-controlled regioselective method for *α*-monobromination, dibromination or imidation of 1,3-diketones with *N*-bromosuccinimide under simple reaction conditions. The employment of solvents plays a key role on the reaction selectivity providing *α*-monobrominated, dibrominated and imidated products. Visible light irradiation accelerates the dibromination reaction of 1,3-diketones. In particular, one important solvent was found to be highly effective for the imidation of 1,3-diketones under base-free condition.

Introduction

Over the past years, extensive attention has been paid to bromination reactions of carbonyl compounds due to their importance in the synthesis of brominated carbonyl compounds which are known as useful building blocks in the synthesis of natural products and pharmaceuticals.[1] Particularly, bromo-functionalities exist widely in many industrially valuable products such as pesticides, herbicides, fire retardants and various new materials.[2] In addition, related research shows that bromination at the reactive position in a 1,3-ketone compound enhances bioactivity like cytotoxicity against breast cancer 1A9 cells compared with unsubstituted compound.[3]

The traditional reagents for *α*-bromination of 1,3-diketones include molecular bromine,[4] NBS[5] and cupric bromide.[6] In terms of accessibility and ease of handing, NBS possesses many advantages. For example, the byproduct succinimide can be easily recovered and reconverted to NBS for subsequent reactions. Normally, some radical initiators such as azobisisobutyronitrile (AIBN) or dibenzoyl peroxide (BPO),[7] or other additives,[8] were required for α-bromination of ketones with NBS. Various improved variants of such reaction system have recently been developed. Typical examples are NBS-NH_4OAc,[8b] NBS-photochemical,[9] NBS-PTSA,[10] NBS-silica supported $NaHCO_3$,[11] NBS-Amberlyst-15,[12] NBS-Lewis acids,[8a] NBS-ionic liquids,[13] among others.[14] Although notable advances have been addressed to the bromination of 1,3-diketones,[15] however, selective *α*-mono or dibromination still remains as a big challenge, especially for the substrates without α-substituents.[1d,8a]

Importantly, *α*-amido *β*-dicarbonylcompounds are widely used as organic intermediates in the synthesis of various heterocycles,[16] peptide mimetics,[17] *α*-amino acids.[18] Classical methods for the synthesis of *α*-amido *β*-dicarbonylcompounds include strong base mediated acylation of the ketimine derivatives of *α*-aminoesters[19] and the reduction of *α*-hydroxyimino[20] and phenylazo[21] *β*-dicarbonyl compounds; the hydrolysis of oxazole-4-carboxylate derivatives;[22] and N–H insertion of metal carbenes.[23] In addition, direct *α*-amination of the readily available *β*-dicarbonylcompounds has been investigated, including electrophilic amination of *β*-dicarbonylcompounds to azodicarboxylates[24] and the *N*-selective nitrosoaldol reaction.[25] Despite the significant advances made in the field,[26] it is still highly desirable to develop new and efficient methods for the direct *α*-amination of the readily available *β*-dicarbonylcompounds.

Recently, NBS has been extensively investigated for the imidation of various ketone compounds such as 1,3-dicarbonyl compounds, phenyl ketones and chalcones,[27] in which an organic base [1,8-diazabicyclo(5.4.1)undec-7-ene] was required for the activation of NBS. Herein, we report a solvent-controlled *α*-monobromination, dibromination or imidation of 1,3-diketones with NBS under simple base-free reaction conditions.[28]

Results and Discussion

At first, we initiated the study on the bromination reaction of 1,3-diphenyl-1,3-propanedione (**1a**) in the presence of 2.0 equivalents of NBS by heating at 110°C under dioxygen atmosphere (Table 1). Preliminary experiments with various solvents were screened for their influence on the reaction behaviour (Table 1, entries 1-5). No dibrominated product **2a** was observed when DMSO or dioxane was used in the reaction. Instead, only low yields of monobrominated product **3a** was obtained (Table 1, entries 1 and 2). The reaction in DMF and toluene provided product **2a** in 36% and 41% yields with a little product **3a**, respectively (Table 1, entries 3 and 4). Later, we focused on the transformation affording dibrominated product **2a**. The yield of **2a** was increased to 51% when acetonitrile was used as the medium (Table 1, entry 5). Replacement of dioxygen with air or argon led to a minor change of yield (Table 1, entries 6 and 7). Lower temperature was better for the reaction, yielding product **2a** in 60% yield (Table 1, entry 8). Finally, the yield of **2a** was enhanced to 82% yield by introducing visible light irradiation to the reaction and increasing the loading of **1a** to 2.5 equiv (Table 1, entry 9). It is noteworthy that the monobrominated product **3a** was formed in very low yields in all the above entries. To our delight, 1,3-diketone was exclusively monobrominated to afford product **3a** in 95% yield at 25°C when the reaction was performed using triethylorthoformate (TOF) as a solvent under air atmosphere (Table 1, entry 10). An imidated product 4a was afforded in 74% yield when the reaction was performed at 130°C and the yield increased to 95% under argon atmosphere instead (Table 1, entry 11). Lowering the reaction temperature influenced the reaction obviously (Table 1, entry 12). Other tested solvents such DMSO, dioxane, DMF, toluene or CH_3CN were all ineffective for this reaction (Table 1, entry 13). Other imdation reagents *N*-iodosuccinimide (NIS) and *N*-chlorosuccinimide (NCS) were also investigated in the reaction,

[a] The Key Laboratory of Carbohydrate Chemistry and Biotechnology, Ministry of Education, School of Biotechnology, School of Pharmaceutical Sciences, Jiangnan University, Lihu Avenue 1800, Wuxi 214122, P.R. China
E-mail: zoulianghua@jiangnan.edu.cn; zwu@jiangnan.edu.cn
[b] State Key Laboratory of Coordination Chemistry, Collaborative Innovation Center of Chemistry for Life Sciences, School ofChemistry and Chemical Engineering, Nanjing University, Xianlin Avenue 163, Nanjing 210093, P. R. China

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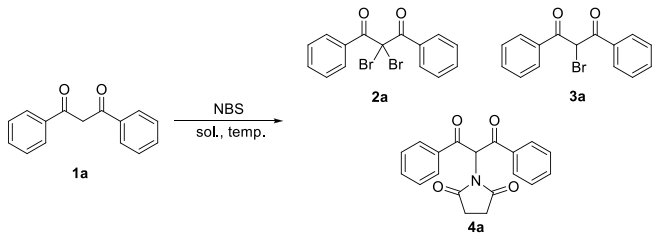
albeit provided product **4a** in lower yields (Table 1, entries 14 and 15).

Table 1. Optimization on reaction conditions.[a]

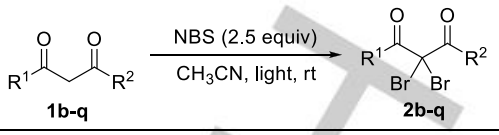


Entry	Solvent	Temp. (°C)	Yield[b] (%) 2a	3a	4a
1	DMSO	110	0	20	0
2	dioxane	110	0	25	0
3	DMF	110	36	15	0
4	toluene	110	41	10	0
5	CH_3CN	110	51	15	0
6	CH_3CN	110	46[c]	8	0
7	CH_3CN	110	55[d]	6	0
8	CH_3CN	55	60[d]	3	0
9	CH_3CN	25	82[d,e]	5	0
10	TOF	25	0	95[c]	0
11	TOF	130	0	0	74[c],95[d]
12	TOF	110	0	0	65[d]
13	TOF	110	0	0	0[d,f]
14	TOF	130	0	0	54[d,g]
15	TOF	130	0	0	15[d,h]

[a]Reaction conditions: **1a** (0.5 mmol), NBS (1 mmol), solvent (2 mL), stirred for 12 h under dioxygen atmosphere. [b]Isolated yield. [c]Air atmosphere. [d]Argon atmosphere. [e]Using 40 W fluorescent lamp and 2.5 equivalents of NBS. [f]Using DMSO, dioxane, DMF, toluene or CH_3CN as solvent instead of TOF. [g]Replacement of NBS with NIS. [h]Replacement of NBS with NCS. TOF: triethylorthoformate. NBS: *N*-Bromosuccinimide. NIS: *N*-Iodosuccinimide. NCS: *N*-Chlorosuccinimide.

With the optimized reaction conditions in hand (see entry 9, Table 1), the scope of the dibromination of 1,3-diketones was investigated and the results were summarized in Table 2. At first, various symmetrical 1,3-diaryl-1,3-propanediones **1b**-**1f** bearing various electron-rich or electron-deficient aromatic groups were employed. For example, Me-, MeO-, Cl-, F- and CF_3- groups were well tolerated in the reaction, providing products **2b**-**2f** in yields ranging from 60% to 85% (Table 2, entries 1-5). Apparently, diketones containing electron-deficient substituents such as -F and $-CF_3$ gave lower yields. Subsequently some unsymmetrical 1,3-diaryl-1,3-propanediones **1g-1j** were also treated under the conditions, affording products **2g-2j** in good yields (Table 2, entries 6-9). To further extend the substrate scope, alkyl substituents were introduced to 1,3-diketones. Initially, substrates **1k-1o** containing an aryl group and an alkyl group were reacted under the optimized reaction conditions, providing products **2k**-**2o** in good yields (Table 2, entries 10-14). One example **1p** with two alkyl groups was also tried in the reaction, giving the desired product **2p** in a fair yield of 55% (Table 2, entry 15). Furthermore, the methodology was effectively applied to a heterocycle 1,3-diketone **1q** as well, yielding product **2q** in good yield of 81% (Table 2, entry 16).

Table 2. Dibronomination of 1,3-diketones in acetonitrile.[a]

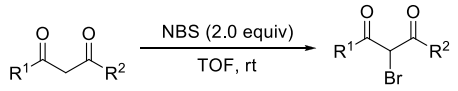


Entry	R^1	R^2	Prod.	Yield (%)
1	*p*-Tol	*p*-Tol	**2b**	80
2	*p*-MeO-C_6H_4	*p*-MeO-C_6H_4	**2c**	79
3	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	**2d**	85
4	*p*-F-C_6H_4	*p*-F-C_6H_4	**2e**	75
5	*p*-CF_3-C_6H_4	*p*-CF_3-C_6H_4	**2f**	60
6	Ph	*p*-Tol	**2g**	75
7	*p*-Tol	*p*-MeO-C_6H_4	**2h**	82
8	*p*-Cl-C_6H_4	*p*-MeO-C_6H_4	**2i**	85
9	*p*-Tol	2-Naphth	**2j**	84
10	*p*-Tol	Me	**2k**	82
11	*p*-MeO-C_6H_4	Me	**2l**	75
12	2-Naphth	Me	**2m**	75
13	*p*-Br-C_6H_4	Me	**2n**	76
14	*p*-CF_3-C_6H_4	Me	**2o**	80
15	EtO	EtO	**2p**	55
16	2-Thienyl	Me	**2q**	81

[a]Reaction conditions: Diketone **1b-q** (0.5 mmol), NBS (1.25 mmol), CH_3CN (2 mL), stirred with a 40 W fluorescent lamp at room temperature for 12 h.

Next the scope of the monobromination of 1,3-diketones was investigated under the optimized reaction conditions (see Table 1,entry 10) and the results were summarized in Table 3. Symmetrical 1,3-diaryl-1,3-propanediones **1b** and **1c** were efficiently employed in the procedure, providing the corresponding

Table 3. Monobronomination of 1,3-diketones in TOF.[a]



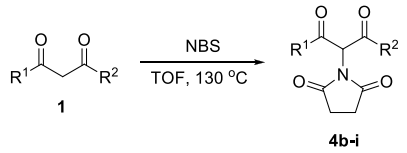
Entry	R^1	R^2	Prod.	Yield (%)
1	*p*-Tol	*p*-Tol	**3b**	80
2	*p*-MeO-C_6H_4	*p*-MeO-C_6H_4	**3c**	81
3	Ph	*p*-Tol	**3d**	90
4	*p*-Tol	*p*-MeO-C_6H_4	**3e**	90
5	*p*-Cl-C_6H_4	*p*-OMe-C_6H_4	**3f**	75
6	*p*-MeO-C_6H_4	Me	**3g**	75

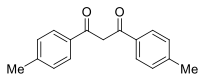
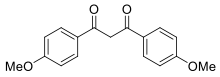
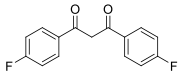
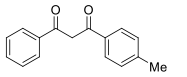
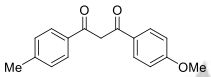
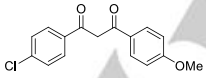
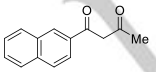
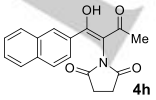
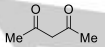
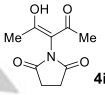
[a]Reaction conditions: Diketone **1** (0.5 mmol), NBS (1 mmol), TOF (2 mL), stirred at room temperature for 12 h. TOF: triethylorthoformate.

products **3b** and **3c** in 80% and 81% yields, respectively (Table 3, entries 1-2). Unsymmetrical substrates **1g**, **1h** and **1i** were also reacted well, affording products **3d**, **3e** and **3f** in good to excellent yields (Table 3,entries 3-5). In addition, one substrate containing an aryl group and an alkyl group was tried under the optimized reaction conditions as well, providing product **3g** in 75% yield (Table 3, entry 6).

Finally, the scope of 1,3-diketones imidation was investigated (Table 4). Symmetrical 1,3-diaryl-1,3-propanedioneswith Me-, MeO- and F- substituents reacted well with *N*-bromosuccinimide to provide the corresponding products **4b**, **4c** and **4d** in 98%, 86% and 85% yields, respectively (Table 4, entries 1-3). Unsymmetrical substrates were also employed in the procedure, affording products **4e**, **4f** and **4g** in good to excellent yields (Table 4, entries 4-6). In all these cases, the products were obtained in ketone form. Interestingly, when substrate containing an aryl group and an alkyl group was utilized under the optimized reaction conditions, enol product **4h** (in complete enol from) was produced in 70% yield (Table 4, entry 7). In addition, another enol product **4i** (in complete enol from) was also obtained in a good yield of 82% when one substrate containing two alkyl groups was used (Table 4, entry 8).

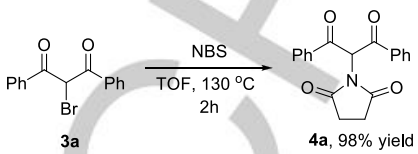
Table 4. The scope of imidation of 1,3-diketones.[a]



Entry	Substrate	Product	Yield (%)
1		**4b**	98
2		**4c**	86
3		**4d**	85
4		**4e**	93
5		**4f**	96
6		**4g**	88
7		 **4h**	70
8		 **4i**	82

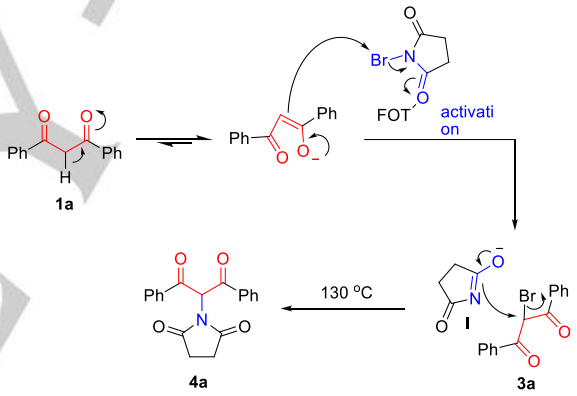
[a]Reaction conditions: Diketone **1** (0.5 mmol), NBS (1 mmol), TOF (2 mL), stirred at 130°C for 12 h. TOF: triethylorthoformate.

In this work, solvent effect played an important role in the transformations between 1,3-diketones and NBS under minor changed reaction conditions. Considering the monobrominated product **3a** might be the intermediate for the synthesis of the imidated product **4a**, one experiment was carried out using **3a** as substrate under optimized reaction conditions (Scheme 1). Indeed, the reaction time could be shortened to 2 hours, providing the desired product **4a** in 98% yield, which demonstrated the excellent selectivity of the reactions in TOF.



Scheme 1. Imidation of **3a** with NBS.

We assumed that α-monobromination or dibromination of 1,3-diketones mainly depended on the solvent effect. A possible mechanism for the imidation reaction was proposed as shown in Scheme 2. In order to elaborate easily, take the synthesis of **4a** as one example. The mechanism may include the promotion of enolate formation[29] and the activation of NBS[30] via hydrogen bonds with the aid of the solvent TOF, simultaneously. The latter involves the formation of an active intermediate **I**, which reacts with **3a** to produce the final product **4a**.



Scheme 2. Proposed mechanism.

Conclusions

In summary, we have developed a solvent-controlled switchable method for *α*-monobromination, dibrominationor imidation of 1,3-diketones with NBS under simple reaction conditions, providing *α*-monobrominated, dibrominated or imidated products by adjusting the reaction medium. Visible light could efficiently promote the dibromination reaction. No base was required for the imidation reaction with the aid of a special solvent. The reaction has a broad substrate scope and is easy to handle, providing practical routes to these divergent diketone derivatives.

Experimental Section

Representative procedure for the synthesis of product **2a** starting from propanedione **1a**: A 10 mL sealed tube equipped with a magnetic stirring bar was charged with all solid components (if liquid, added after flushed with argon) including **1a** (112.0 mg, 0.5 mmol), NBS (222.5 mg, 1.25 mmol). The aperture of the tube

was then covered with a rubber septum, and purged with argon flow for 5 minutes. After the addition of acetonitrile (2 mL) by syringe, the septum was quickly replaced by a teflon-coated screw cap, and the reaction vessel was placed under visible light (40 W fluorescent lamp) at room temperature and stirred for 12 h, and then diluted with ethyl acetate. The resulting solution was directly concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate = 50:1) gave **2a** as a white solid in 82% yield (156.6. mg, 0.41 mmol).

Representative procedure for the synthesis of product **3a** starting from propanedione **1a**: A 10 mL sealed tube equipped with a magnetic stirring bar was charged with all solid or liquid components including **1a** (112.0 mg, 0.5 mmol), NBS (177.8 mg, 1.0 mmol). After the addition of triethylorthoformate (2 mL) by syringe, the reaction vessel was placed under air at room temperature and stirred for 12 h, and then diluted with ethyl acetate. The resulting solution was directly concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate = 10:1) gave **3a** as a white solid in 95% yield (144.0 mg, 0.48 mmol).

Representative procedure for the synthesis of product **4a** starting from propanedione **1a**: A 10 mL sealed tube equipped with a magnetic stirring bar was charged with all solid components (if liquild, added after flushed with argon) including **1a** (112.0 mg, 0.5 mmol), NBS (177.8 mg, 1.0 mmol). The aperture of the tube was then covered with a rubber septum, and purged with argon flow for 5 minutes. After the addition of triethylorthoformate (2 mL) by syringe, the septum was quickly replaced by a teflon-coated screw cap, and the reaction vessel was moved to a pre-heated device at 130°C and stirred for 12 h, and then diluted with ethyl acetate. The resulting solution was directly concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate = 2:1) gave **4a** as a white solid in 95% yield (152.6. mg, 0.475 mmol).

Acknowledgements

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Keywords: 1,3-Diketones • Monobromination • Dibromination • Base-free • Selectivity

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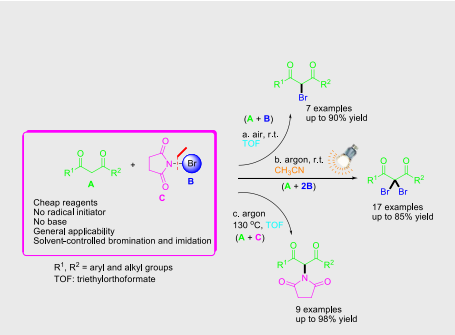

A solvent-controlled regioselective method for *α*-monobromination, *α,α*-dibromination or imidation of 1,3-diketones was developed with *N*-bromosuccinimide. Dibromination of 1,3-diketones took place efficiently in acetonitrile with the aid of visible light irradiation. One important solvent triethylorthoformate was found to be highly effective for the monobromination of 1,3-diketones, as well as an ideal medium for the imidation reaction under base-free condition.

Selective Functionization

Liang-Hua Zou,* Yan-Chun Li, Ping-Gui Li, Jing Zhou, and Zhimeng Wu*

Page No. – Page No.

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