

# Organic synthesis using (diacetoxyiodo)benzene (DIB): Unexpected and novel oxidation of 3-oxo-butanamides to 2,2-dihalo-*N*-phenylacetamides

Wei-Bing Liu<sup>\*1</sup>, Cui Chen<sup>1</sup>, Qing Zhang<sup>1</sup> and Zhi-Bo Zhu<sup>\*2</sup>

## Full Research Paper

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### Address:

<sup>1</sup>School of Chemistry and Life Science, Guangdong University of Petrochemical Technology, Maoming 525000, China and <sup>2</sup>College of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, China

### Email:

Wei-Bing Liu<sup>\*</sup> - lwb409@yahoo.com.cn; Zhi-Bo Zhu<sup>\*</sup> - zzb24@yahoo.com.cn

\* Corresponding author

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## Abstract

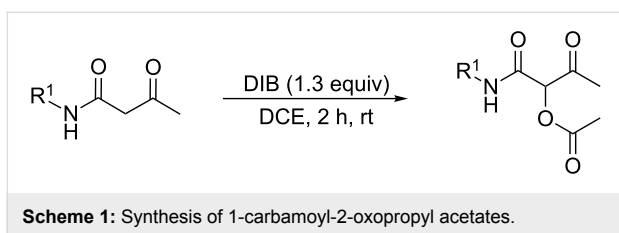
A novel and reliable method for the direct preparation of 2,2-dihalo-*N*-phenylacetamides is reported. The key transformation involves the cleavage of a carbon–carbon bond in the presence of DIB and a Lewis acid as the halogen source, and thus this method significantly expands the value of DIB as a unique and powerful tool in chemical synthesis. This protocol not only adds a new aspect to reactions that use other hypervalent iodine reagents but also provides a wide space for the synthesis of disubstituted acetamides.

## Introduction

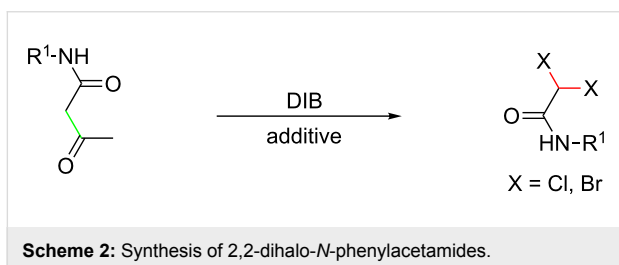
Hypervalent iodine(III) reagents [1–18] have received much attention, as reflected by the plethora of publications and reviews [19–23]. This is due to their low toxicity, ready availability, easy handling, clean transformation, and reactivity, which is similar to heavy-metal-based oxidants, including harmful elements, such as Pb(IV), Hg(II), and Tl(III), as well as transition metal-catalyzed processes [24–30]. Recently, we reported an efficient acetoxylation approach to synthesize

1-carbamoyl-2-oxopropyl acetate derivatives by using (diacetoxyiodo)benzene (DIB) (Scheme 1) [31].

During the course of conditional optimization to synthesize 1-carbamoyl-2-oxopropyl acetate derivatives, we surprisingly found that almost none of the desired acetoxylation product was obtained, but 2,2-dichloro-*N*-phenylacetamide was provided as the major product, upon addition of Lewis acids such as FeCl<sub>3</sub>,



ZnCl<sub>2</sub> and CuCl<sub>2</sub> in the reaction system. Based on this result, we developed a simple and efficient approach to the synthesis of 2,2-dihalo-*N*-phenylacetamides, on which we report herein (Scheme 2). To the best of our knowledge, there are several reports on chlorination and bromination reactions with PhI(OAc)<sub>2</sub> and a halogen source such as TMSBr, lithium halide or pyridinium halide [32–34]. Also, there are several reports on the synthesis of difunctionalized acetamide derivatives [35–38], but this report is the first to describe the synthesis of 2,2-dihalo-*N*-phenylacetamides through an oxidative process with PhI(OAc)<sub>2</sub> and Lewis acids as the halogen source.



## Results and Discussion

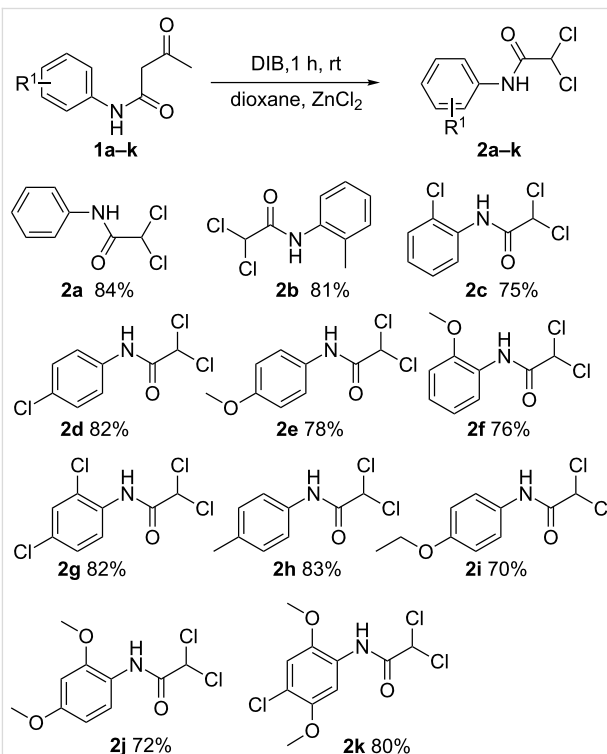
Initially, we used 3-oxo-*N*-phenylbutanamide (**1a**) as the model substrate to optimize the reaction conditions in different solvents, temperatures and amounts of DIB (Table 1). The best result was obtained in dioxane in the presence of 1.3 equiv of DIB and 1.5 equiv of zinc(II) chloride at room temperature for one hour (Table 1, entry 11). For this transformation, FeCl<sub>3</sub> and ZnCl<sub>2</sub> were suitable Lewis acids (Table 1, entry 2 and entry 3), and dioxane and DMF were practical solvents among the various solvents examined (Table 1, entry 3 and entry 8). It is noteworthy that no product **2a** was obtained when the reaction was carried out without the addition of Lewis acids (Table 1, entry 1) or without DIB (Table 1, entry 5).

After optimizing the reaction conditions, we used a range of 3-oxo-*N*-phenylbutanamides to explore the substrate scope and limitations of this reaction. As shown in Scheme 3, all the reactions proceeded smoothly and gave the corresponding *N*-phenyl dichloroacetamides **2a–2k** exclusively and in good to excellent isolated yields. It was also found that the number and the electronic properties of the substituents on the benzene ring had little effect on the reaction. For example, the reactions of 3-oxo-

**Table 1:** Optimization of reaction conditions.<sup>a</sup>

entry	solvent	additive (1.5 equiv)	time (h)	yield (%) <sup>b</sup>
1	dioxane	none	1	–
2	dioxane	FeCl <sub>3</sub>	1	78
3	dioxane	ZnCl <sub>2</sub>	1	81
4 <sup>c</sup>	dioxane	ZnCl <sub>2</sub>	1	75
5 <sup>d</sup>	dioxane	ZnCl <sub>2</sub>	1	–
6	cyclohexane	ZnCl <sub>2</sub>	1	26
7	DCE	ZnCl <sub>2</sub>	1	42
8	DMF	ZnCl <sub>2</sub>	1	80
9	DMSO	ZnCl <sub>2</sub>	1	46
10 <sup>e</sup>	dioxane	ZnCl <sub>2</sub>	1	31
11 <sup>f</sup>	dioxane	ZnCl <sub>2</sub>	1	89
12 <sup>g</sup>	dioxane	ZnCl <sub>2</sub>	1	84
13 <sup>f</sup>	dioxane	ZnCl <sub>2</sub>	0.5	53
14 <sup>f</sup>	dioxane	ZnCl <sub>2</sub>	1.5	89
15 <sup>f</sup>	dioxane	ZnCl <sub>2</sub>	2	89

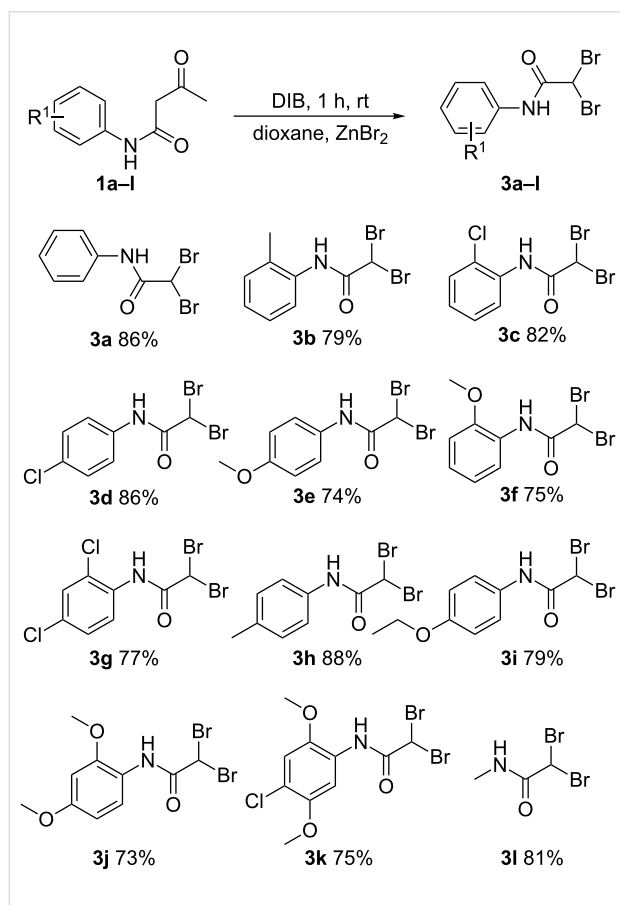
<sup>a</sup>**1a** (0.25 mmol), solvent (2 mL), DIB (1.0 equiv); <sup>b</sup>GC yield; <sup>c</sup>ZnCl<sub>2</sub> (1.0 equiv); <sup>d</sup>without DIB; <sup>e</sup>DIB (0.5 equiv); <sup>f</sup>DIB (1.3 equiv); <sup>g</sup>DIB (2.0 equiv).



**Scheme 3:** Synthesis of dichloroacetamides. Reagents and conditions: **1** (1.0 mmol), dioxane (2 mL), DIB (1.3 equiv), ZnCl<sub>2</sub> (1.5 equiv); yields % are isolated yields.

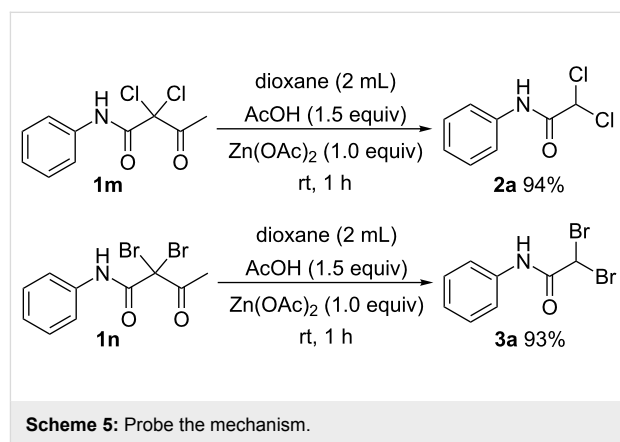
*N*-phenylbutanamide (**1a**), 3-oxo-*N*-*o*-tolylbutanamide (**1b**), *N*-(2,4-dimethoxyphenyl)-3-oxobutanamide (**1j**) and *N*-(4-chloro-2,5-dimethoxyphenyl)-3-oxobutanamide (**1k**) all led to their corresponding *N*-phenyl dichloroacetamides (Scheme 3, **2a**, **2b**, **2j**, and **2k**) in good isolated yields. In addition, the position of the substituents on the benzene ring also has little effect on this transformation, such that *N*-(2-chlorophenyl)-3-oxobutanamide (**1c**), *N*-(4-chlorophenyl)-3-oxobutanamide (**1d**), *N*-(4-methoxyphenyl)-3-oxobutanamide (**1e**) and *N*-(2-methoxyphenyl)-3-oxobutanamide (**1f**) could also serve as good substrates in this protocol (Scheme 3, **2c**, **2d**, **2e**, and **2f**).

Next, in order to expand the scope of this protocol, we employed ZnBr<sub>2</sub> as a reagent under the same reaction conditions, and we were pleased to find that the corresponding dibromo derivatives were obtained as the products. As shown in Scheme 4, all tested substrates provided the corresponding dibromoacetamides **3a–3l** in good to excellent isolated yields, which not only greatly expanded the application scope of this protocol but also provided a wide space for the synthesis of 2,2-dihalo-*N*-phenylacetamides.



**Scheme 4:** Synthesis of dibromoacetamides. Reagents and conditions: **1** (1.0 mmol), dioxane (2 mL), DIB (1.3 equiv), ZnBr<sub>2</sub> (1.5 equiv); yields % are isolated yields.

In spite of the widespread use of DIB, there is no direct precedent for DIB-mediated cleavage of C–C bonds. In particular, the application of this protocol to synthesize difunctionalized acetamides from 3-oxo-butanamides is reported here for the first time. In order to probe the mechanism of this transformation, we employed 2,2-dichloro-3-oxo-*N*-phenylbutanamide (**1m**) and 2,2-dibromo-3-oxo-*N*-phenylbutanamide (**1n**) as reactants under acidic conditions in the presence of Zn(OAc)<sub>2</sub> (Scheme 5), and we found that the reaction can also give the corresponding product 2,2-dichloro-*N*-phenylacetamide (**2a**) and 2,2-dibromo-*N*-phenylacetamide (**3a**).

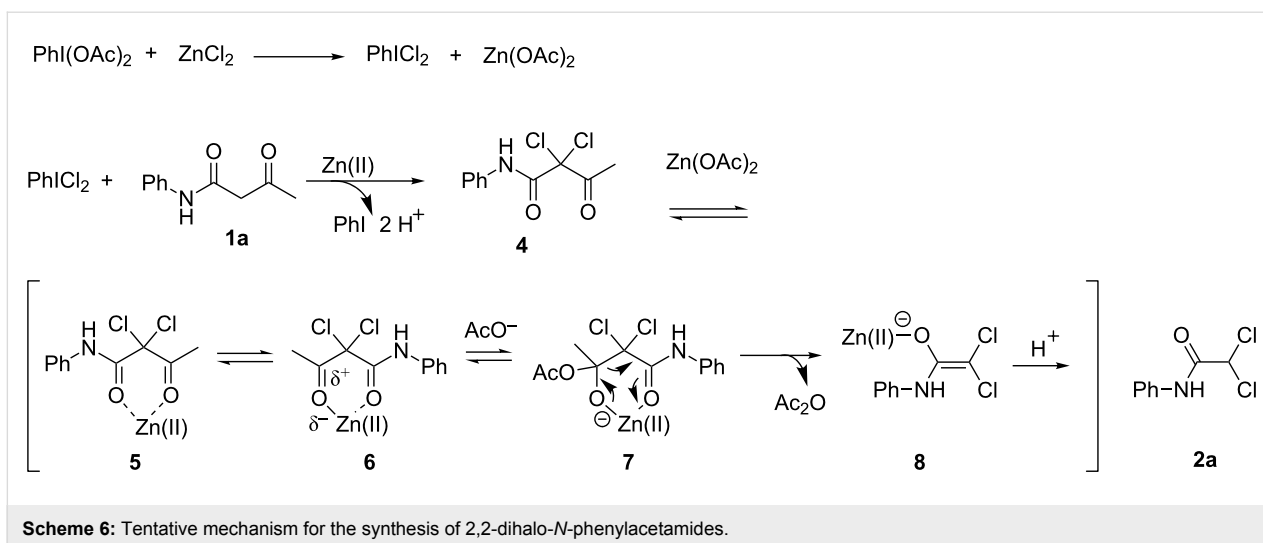


**Scheme 5:** Probe the mechanism.

On the basis of these preliminary results, a mechanistic proposal for this transformation, exemplified by the formation of **2a**, is depicted in Scheme 6. Initially, the reaction involved generation of the known chlorinating agent (dichloroiodo)benzene (PhICl<sub>2</sub>) [39], followed by dichlorination of the β-keto amide of 3-oxo-*N*-phenylbutanamide (**1a**) to give intermediate **4**. It is well known that Lewis acids can activate 1,3-diketones [40] to produce intermediate **5** and **6**. This complexation not only increases the nucleophilicity of the methylene carbon atom, but also simultaneously increases the electrophilicity of the carbonyl carbon atom. Consequently, nucleophilic attack of the acetate ion on the carbonyl carbon atom affords intermediate **7**. A subsequent carbon–carbon bond cleavage of the labile α,α-dichloro β-keto amide through a retro-Claisen condensation reaction [41] generates intermediate **8**. Finally, the electrophilic attack of a proton on the carbon–carbon double bond resulted in the final product 2,2-dichloro-*N*-phenylacetamide (**2a**).

## Conclusion

In summary, we have shown an efficient and operationally simple method to synthesize 2,2-dihalo-*N*-phenylacetamides. The mild reaction conditions, good substrate scope and good to excellent yields make the present protocol potentially useful in organic synthesis. Moreover, it should be pointed out that this transformation includes an oxidative process involving the



cleavage of a carbon–carbon bond, which significantly expands the value of DIB as a unique and powerful tool in chemical synthesis. Future studies on the application of this protocol to the synthesis of other difunctionalized acetamides and detailed investigations of the reaction mechanism are in progress.

## Supporting Information

### Supporting Information File 1

Experimental details and characterization of compounds.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-38-S1.pdf>]

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## References

- Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358. doi:10.1021/cr800332c
- Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656–3665. doi:10.1002/anie.200500115
- Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893–2903. doi:10.1021/jo050117b
- Ladziata, U.; Zhdankin, V. V. *ARKIVOC* **2006**, (ix), 26–58.
- Zhdankin, V. V. *ARKIVOC* **2009**, (i), 1–62.
- Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073–2085. doi:10.1039/b821747e
- Yusubov, M. S.; Zhdankin, V. V. *Mendeleev Commun.* **2010**, *20*, 185–191. doi:10.1016/j.mencom.2010.06.001
- Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086–2099. doi:10.1039/b823399c
- Ngatimin, M.; Lupton, D. W. *Aust. J. Chem.* **2010**, *63*, 653–658. doi:10.1071/CH09625
- Yusubov, M. S.; Nemykin, V. N.; Zhdankin, V. V. *Tetrahedron* **2010**, *66*, 5745–5752. doi:10.1016/j.tet.2010.04.046
- Satam, V.; Harad, A.; Rajule, R.; Pati, H. *Tetrahedron* **2010**, *66*, 7659–7706. doi:10.1016/j.tet.2010.07.014
- Uyanik, M.; Ishihara, K. *Aldrichimica Acta* **2010**, *43*, 83–91.
- Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052–9070. doi:10.1002/anie.200904689
- Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517–538. doi:10.1055/s-0030-1258328
- Desjardins, S.; Andrez, J. C.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406–3409. doi:10.1021/ol201149u
- Singh, F. V.; Wirth, T. *Org. Lett.* **2011**, *13*, 6504–6507. doi:10.1021/ol202800k
- Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410–16413. doi:10.1021/ja207775a
- Guilbault, A.-A.; Legault, C. Y. *ACS Catal.* **2012**, *2*, 219–222. doi:10.1021/cs200612s
- Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179–1255. doi:10.1016/S0040-4020(96)00970-2
- Brand, J. P.; González, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102–115. doi:10.1039/c0cc02265a
- Niedermann, K.; Früh, N.; Vinogradova, E.; Wiehn, M. S.; Moreno, A.; Togni, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1059–1163. doi:10.1002/anie.201006021
- Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175–2177. doi:10.1002/anie.200907352
- Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4332–4336. doi:10.1002/anie.200900974
- Ochiai, M.; Miyamoto, K. *Eur. J. Org. Chem.* **2008**, 4229–4239. doi:10.1002/ejoc.200800416
- Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402–4404. doi:10.1002/anie.200601817
- Kita, Y.; Tohma, H.; Yakura, T. *Trends Org. Chem.* **1992**, *3*, 113–128.
- Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627–630. doi:10.1351/pac199668030627
- Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178. doi:10.1021/cr940424+
- Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584. doi:10.1021/cr010003+

30. Tohma, H.; Kita, Y. *J. Synth. Org. Chem., Jpn.* **2004**, *62*, 116–127.
31. Liu, W.-B.; Chen, C.; Zhang, Q.; Zhu, Z.-B. *Beilstein J. Org. Chem.* **2011**, *7*, 1436–1440. doi:10.3762/bjoc.7.167
32. Evans, P. A.; Brandt, T. A. *J. Org. Chem.* **1997**, *62*, 5321–5326. doi:10.1021/jo970525i
33. Ngatimin, M.; Gartshore, C. J.; Kindler, J. P.; Naidu, S.; Lupton, D. W. *Tetrahedron Lett.* **2009**, *50*, 6008–6011. doi:10.1016/j.tetlet.2009.08.038
34. Hamamoto, H.; Hattori, S.; Takemaru, K.; Miki, Y. *Synlett* **2011**, 1563–1566. doi:10.1055/s-0030-1260791
35. Pasquato, L.; Santoni, G.; Modena, G. *Eur. J. Org. Chem.* **2001**, 3457–3460. doi:10.1002/1099-0690(200109)2001:18<3457::AID-EJOC3457>3.0.CO;2-C
36. Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2010**, *12*, 1492–1495. doi:10.1021/ol100196a
37. Fujii, T.; Izumi, K.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1055–1056. doi:10.1246/bcsj.58.1055
38. Katagiri, N.; Niwa, R.; Furuya, Y.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1833–1841. doi:10.1248/cpb.31.1833
39. Paquette, L. A., Ed. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995; Vol. 6, p 3984.
40. Christoffers, J. *Chem. Commun.* **1997**, 943–944. doi:10.1039/a700838d
41. Biswas, S.; Maiti, S.; Jana, U. *Eur. J. Org. Chem.* **2010**, 2861–2866. doi:10.1002/ejoc.201000128

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