

Direct construction of 5-methyl-2-phenylisoxazol-3(2H)-ones via hypervalent iodine mediated sequential tandem oxidative cyclization of 3-oxo-*N*-phenylbutanamides catalyzed by zinc oxide (ZnO)[†]Cite this: *Org. Biomol. Chem.*, 2013, **11**, 542Received 4th November 2012,
Accepted 22nd November 2012

DOI: 10.1039/c2ob27145a

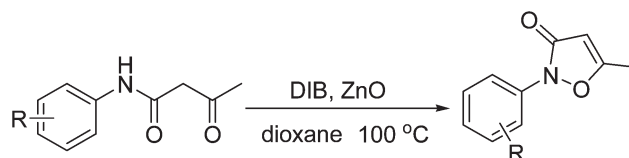
www.rsc.org/obc

Weibing Liu,^{*a} Peng Zhou,^a Cui Chen,^a Qing Zhang^a and Zhibo Zhu^{*b}

A sequential oxidative tandem cyclization reaction mediated by a combination of (diacetoxyiodo)benzene (DIB) with zinc oxide (ZnO) is presented for the synthesis of 5-methyl-2-phenylisoxazol-3(2H)-ones from β -ketobutylanilides. A variety of β -ketobutylanilide compounds were used in this approach, and a wide range of functionalized 5-methylisoxazol-3(2H)-ones were obtained in good to excellent yields.

Introduction

Heterocycles feature prominently in pharmaceuticals, agrochemicals, organic intermediates and novel materials and this has provided a driving force for synthetic organic and pharmaceutical chemists to develop increasingly efficient methods toward their synthesis.¹ The construction of many heterocyclic molecules traditionally required several substrates or reagents.² Substrates with several reactive positions in the same molecule, such as β -ketobutylanilides, have provided advantageous alternatives for the synthesis of heterocycles. We can regulate the different reactive positions to construct many different five- and six-membered nitrogen- or oxygen-containing heterocyclic compounds. β -Ketobutylanilides are a typical representative, and recently there have been several reports about the synthesis of several heterocyclic compounds using β -ketobutylanilides as the only substrate.³ In this communication, we report a novel method for the direct construction of 5-methyl-2-phenylisoxazol-3(2H)-ones via (diacetoxyiodo)benzene (DIB)-mediated sequential oxidative tandem cyclization of β -ketobutylanilides catalyzed by zinc oxide (ZnO) (Scheme 1). As is well known, isoxazole is an important



Scheme 1 Synthesis of 5-methyl-2-phenylisoxazol-3(2H)-ones.

structure and synthon, due to the occurrence of this unit in many molecules that are of biological and pharmaceutical interest.⁴

Results and discussion

Initially 3-oxo-*N*-phenylbutanamide **1a** was selected as a model substrate to optimize the reaction conditions (Table 1). The results showed that this transformation did not occur in the absence of zinc oxide (ZnO) (Table 1, entry 1). Notable efficacy was achieved for this reaction when increasing the reaction temperature from room temperature to 100 °C, and afforded the desired product 5-methyl-2-phenylisoxazol-3(2H)-one in 61% GC yield (Table 1, entries 2–3). Results of the screening study of the reaction time and the amount of ZnO (Table 1, entries 2, 4–8) indicated that 0.2 equivalent of ZnO was sufficient and 5 h was the optimal reaction time for the completion of the reaction. Among the various solvents examined, dioxane, *N,N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were practical for this transformation (Table 1, entries 4, 9–12).

With the optimized conditions in hand (Table 1, entry 4), we then investigated the substrate scope of this protocol (Scheme 2). A range of 3-oxo-*N*-phenylbutanamides **1a–1j** were all efficiently transformed to their corresponding products **2a–2j** in high to excellent yields. Substrates bearing electron-donating substituents, such as, methyl, methoxyl and ethoxyl, at the *ortho*-, *meta*- or *para*-positions of benzene ring were also smoothly converted to the expected 5-methyl-2-phenylisoxazol-

^aSchool of Chemistry and Life Science, Guangdong University of Petrochemical Technology, 139 of Guangdu Two Road, Maoming 525000, P. R. China.

E-mail: lwb409@yahoo.com.cn; Fax: +86-668-2923575; Tel: +86-668-2923956

^bSchool of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, China. E-mail: zzb24@yahoo.com.cn

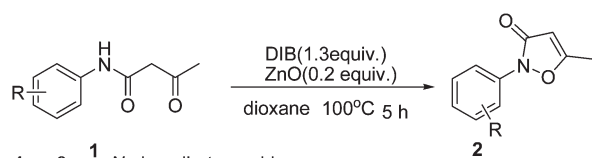
[†]Electronic supplementary information (ESI) available: Full experimental details and copies of NMR spectral data. See DOI: 10.1039/c2ob27145a

Table 1 Optimization of reaction conditions^a

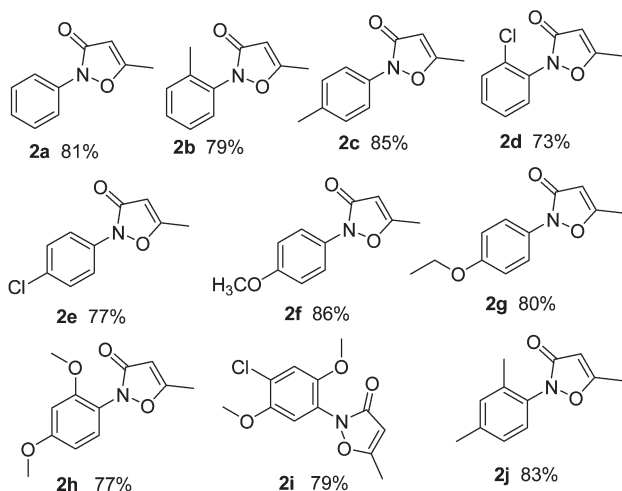
Entry	Solvent	Reaction time (h)	ZnO (equiv.)	Yield ^b (%)
1	Dioxane	3	None	None
2	Dioxane	3	0.2	61
3 ^c	Dioxane	3	0.2	None
4	Dioxane	5	0.2	88
5	Dioxane	7	0.2	88
6	Dioxane	5	0.2	57
7	Dioxane	5	0.5	88
8	Dioxane	5	1.0	88
9	DMF	5	0.2	85
10	DMSO	5	0.2	82
11	DCE (reflux)	5	0.2	72
12	Toluene	5	0.2	33

^a Reaction conditions: **1a** (0.25 mmol), dioxane (2.0 mL). ^b GC yields.

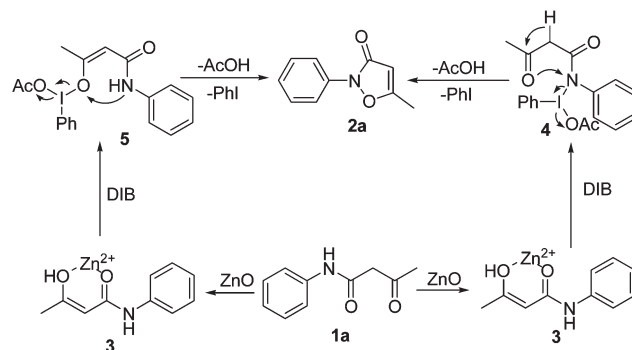
^c Reaction temperature: room temperature.



- 1a** = 3-oxo-*N*-phenylbutanamide
1b = 3-oxo-*N*-*o*-tolylbutanamide
1c = 3-oxo-*N*-*p*-tolylbutanamide
1d = *N*-(2-chlorophenyl)-3-oxobutanamide
1e = *N*-(4-chlorophenyl)-3-oxobutanamide
1f = *N*-(4-methoxyphenyl)-3-oxobutanamide
1g = *N*-(4-ethoxyphenyl)-3-oxobutanamide
1h = *N*-(2,4-dimethoxyphenyl)-3-oxobutanamide
1i = *N*-(4-chloro-2,5-dimethoxyphenyl)-3-oxobutanamide
1j = *N*-(2,4-dimethylphenyl)-3-oxobutanamide

**Scheme 2** Scope of the substrates (notes: all the listed yields are isolated yields).

3(2*H*)-ones. For example, the reactions employing substrates with either monosubstituted (**1b–1g**), disubstituted (**2h, 2j**) or trisubstituted groups **2h–2j** on the benzene ring can all

**Scheme 3** Proposed mechanism.

smoothly provide the expected products **2b–2j** in good to excellent yield.

Plausible reaction pathways have been proposed to account for this transformation, exemplified by the formation of **2a** (Scheme 3). It is well known that Lewis acids can activate 1,3-diketones to produce intermediate **3**.⁵ Therefore, we speculate that the *O,O'*-bound complex **3** is formed initially upon treatment of **1a** with Zn(II).⁶ Then, the nucleophilic nitrogen atom or oxygen atom of **3** interacts with the electrophilic iodine(III) of PhI(OAc)₂,⁷ to form intermediate **4** or **5** by eliminating one equivalent of acetic acid. Subsequent N–I or O–I σ -bond cleavage, along with nucleophilic attack of the carbonylic oxygen atom or nitrogen atom, affords the final product **2a** by eliminating one molecule of iodobenzene and one molecule of acetic acid.

Conclusions

In summary, we have developed an efficient strategy for the direct construction of 5-methyl-2-phenylisoxazol-3(2*H*)-ones *via* a sequential tandem oxidative cyclization of 3-oxo-*N*-phenylbutanamides using a combination of PhI(OAc)₂–ZnO. The reaction is tolerant of a range of functional groups and thus effective for a broad scope of substrates. The current direction for future research is aimed at extending the scope and potential synthetic applications.

References

- (a) J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Blackwell, Oxford, 4th edn, 2000; (b) T. Eicher and S. Hauptmann, *The Chemistry of Heterocycles*, Wiley-VCH, Weinheim, 2003; (c) A. R. Katritzky and A. F. Pozharskii, *Handbook of Heterocyclic Chemistry*, Pergamon, Amsterdam, 2nd edn, 2000; (d) P. A. Renhowe, S. Pecchi, C. M. Shafer, T. D. Machajewski, E. M. Jazan, C. Taylor, W. Antonios-McCrea, C. M. McBride, K. Frazier, M. Wiesmann, G. R. Lapointe, P. H. Feucht, R. L. Warne, C. C. Heise, D. Menezes, K. Aardalen, H. Ye, M. He, V. Le, J. Vora, J. M. Jansen, M. E. Wernette-Hammond and A. L. Harris,

- J. Med. Chem.*, 2009, **52**, 278; (e) M. Wittman, J. Carboni, R. Attar, B. Balasubramanian, P. Balimane, P. Brassil, F. Beaulieu, C. Chang, W. Clarke, J. Dell, J. Eummer, D. Frennesson, M. Gottardis, A. Greer, S. Hansel, W. Hurlburt, B. Jacobson, S. Krishnananthan, F. Y. Lee, A. Li, T.-A. Lin, P. Liu, C. Ouellet, X. Sang, M. G. Saulnier, K. Stoffan, Y. Sun, U. Velaparathi, H. Wong, Z. Yang, K. Zimmermann, M. Zoeckler and D. Vyas, *J. Med. Chem.*, 2005, **48**, 5639; (f) M. Iwakubo, A. Takami, Y. Okada, T. Kawata, Y. Tagami, M. Sato, T. Sugiyama, K. Fukushima, S. Taya, M. Amano, K. Kaibuchi and H. Iijima, *Bioorg. Med. Chem.*, 2007, **15**, 1022; (g) A. Schmidt, A. Beutler and B. Snovdovych, *Eur. J. Org. Chem.*, 2008, 4073; (h) H. Cerecetto, A. Gerpe, M. Gonzalez, V. J. Aran and C. O. de Ocariz, *Mini-Rev. Med. Chem.*, 2005, **5**, 869.
- 2 (a) L. Y. Zheng, Y. Ju, Y. H. Bin and R. M. Hua, *J. Org. Chem.*, 2012, **77**, 5794; (b) C. S. Jeffrey, K. L. Barnes, J. A. Eickhoff and C. R. Carson, *J. Am. Chem. Soc.*, 2011, **133**, 7688; (c) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449; (d) Y. Nishimura, Y. Kawamura, Y. Watanabe and M. Hayashi, *J. Org. Chem.*, 2010, **75**, 3875.
- 3 (a) A. Maiti, P. V. N. Reddy, M. Sturdy, L. Marler, S. D. Pegan, A. D. Mesecar, J. M. Pezzuto and M. Cushman, *J. Med. Chem.*, 2009, **52**, 1873; (b) R. Zhang, D. Y. Zhang, Y. J. Liang, G. Y. Zhou and D. W. Dong, *J. Org. Chem.*, 2011, **76**, 2880; (c) Z. G. Zhang, Q. Zhang, Z. H. Yan and Q. Liu, *J. Org. Chem.*, 2007, **72**, 9808; (d) R. Zhang, D. Y. Zhang, Y. J. Liang, G. Y. Zhou, Z. J. Jiang and D. W. Dong, *J. Org. Chem.*, 2008, **73**, 9504; (e) D. X. Xiang, K. W. Wang, Y. J. Liang, G. Y. Zhou and D. W. Dong, *Org. Lett.*, 2008, **10**, 345; (f) J. M. Knapp, J. S. Zhu, A. B. Wood and M. J. Kurth, *ACS Comb. Sci.*, 2012, **14**, 85.
- 4 (a) P. K. Poutiainen, T. Oravilahti, M. Peräkylä, J. J. Palvimo, J. A. Ihalainen, R. Laatikainen and J. T. Pulkkinen, *J. Med. Chem.*, 2012, **55**, 6316; (b) M. V. Yermolina, J. Z. Wang, M. Caffrey, L. L. Rong and D. C. Wardrop, *J. Med. Chem.*, 2011, **54**, 765; (c) M. H. El-Badri and M. J. Kurth, *J. Comb. Chem.*, 2009, **11**, 228; (d) S. Velaparathi, M. Brunsteiner, R. Uddin, B. J. Wan, S. J. Franzblau and P. A. Petukhov, *J. Med. Chem.*, 2008, **51**, 1999; (e) S. A. Laufer and S. Margutti, *J. Med. Chem.*, 2008, **51**, 2580.
- 5 J. Christoffers, *Chem. Commun.*, 1997, 943.
- 6 J. Yu, S. S. Liu, J. Cui, X. S. Hou and C. Zhang, *Org. Lett.*, 2012, **14**, 832.
- 7 (a) J. Tian, W. C. Gao, D. M. Zhou and C. Zhang, *Org. Lett.*, 2012, **14**, 3020; (b) T. Jen, B. A. Mendelsohn and M. A. Ciufolini, *J. Org. Chem.*, 2011, **76**, 728; (c) E. Malamidou-Xenikaki, S. Spyroudis, M. Tsanakopoulou and D. Hadjipavlou-Litina, *J. Org. Chem.*, 2009, **74**, 7315; (d) W. Q. Yu, Y. F. Du and Z. Zhao, *Org. Lett.*, 2009, **11**, 2417.