ChemComm

View Online / Journal Homepage
Dynamic Article Links

Cite this: DOI: 10.1039/c2cc34561g

www.rsc.org/chemcomm

COMMUNICATION

I_2 promoted domino oxidative cyclization for one-pot synthesis of 2-acylbenzothiazoles *via* metal-free sp^3 C–H functionalization†

Yan-Ping Zhu, Mi Lian, Feng-Cheng Jia, Mei-Cai Liu, Jing-Jing Yuan, Qing-He Gao and An-Xin Wu*

Received 26th June 2012, Accepted 19th July 2012
DOI: 10.1039/c2cc34561g

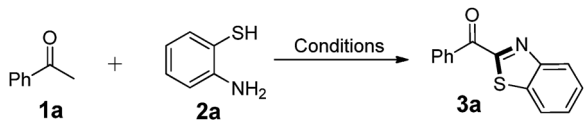
An I_2 promoted domino protocol was developed to construct 2-acylbenzothiazoles from simple and readily available aromatic ketones/unsaturated methyl ketones and *o*-aminobenzenethiols. The reaction proceeded smoothly under metal-free and peroxide-free conditions.

In recent years, catalytic C–H functionalization, especially an sp^3 C–H bond, has drawn considerable interest.[1] Many excellent results have been achieved based on the transition-metal-catalyzed approach. Very recently, iodide catalyzed C–H bond functionalization has been established. For example, the process of quaternary ammonium iodide and TBHP catalyzing C–H activation to construct C–O, C–N bonds and heterocycles was well demonstrated by Ishihara,[2] Nachtsheim,[3] Yu and Han,[4] Wan,[5] and Zhu.[6] I_2 and TBHP promoted functionalization of a C–H bond was also proposed and utilized by Wang,[7] Jiang,[8] Prabhu,[9] and Wang.[10] To further study iodide catalyzed direct C–H bond functionalization further methods are still desirable.

Benzothiazole is an important class of heterocycle, which exists widely in natural products. Many compounds containing a benzothiazole motif exhibit potent biological activities and medicinal significance.[11] Although the synthesis of 2-arylbenzathiazoles has received much interest, 2-acylbenzathiazoles are rarely synthesized due to the difficulty in introducing an acyl group at the 2-position of benzothiazoles. Only a few methods have been reported for the synthesis of 2-acylbenzathiazoles thus far.[12] Herein, we reported a metal-free and peroxide-free I_2 promoted sp^3 C–H bond functionalization protocol to construct 2-acylbenzothiazoles and their derivatives.

To initiate our study, we optimized the reaction conditions for the formation of 2-acylbenzothiazole with acetophenone (**1a**) and 2-aminobenzenethiol (**2a**) as substrates (Table 1). When acetophenone (**1a**, 1 mmol), 2-aminobenzenethiol (**2a**, 1 mmol) were heated at 80 °C in the presence of I_2/CuO (1.1 mmol/1.1 mmol), the desired product could only be obtained in a low yield (Table 1, entry 1). The temperature was subsequently investigated (Table 1, entries 1–3), where 100 °C was found to be the most effective temperature, giving a moderate result (Table 1, entry 3). Upon increasing the dose of I_2 to 2.0 mmol, the yield was slightly increased (Table 1, entry 5). However, surprising results were obtained in the control experiments in which the desired product was observed in good yield in the absence of metal catalyst CuO (Table 1, entry 6). The reaction wholly failed perform in the absence of I_2, or I_2/CuO (Table 1, entries 7–8). These results suggested that I_2 played a crucial role in the transformation. Various solvents were also investigated (see ESI†); DMSO was found to be the most efficient media for the process. After several experimental iterations, the optimal reaction conditions emerged with acetophenone **1a** (1.0 mmol), 2-aminobenzenethiol **2a** (1.2 mmol), and I_2 (1.50 mmol) at 100 °C in DMSO (Table 1, entry 14).

Table 1 Optimization of the reaction conditions[a]



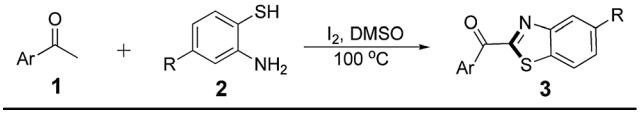
Entry	I_2 (mmol)	CuO (mmol)	Temp (°C)	Time (h)	Yield[b] (%)
1	1.1	1.1	80	2.0	50
2	1.1	1.1	90	2.0	53
3	1.1	1.1	100	1.5	62
4	1.5	1.1	100	1.5	72
5	2.0	1.1	100	1.5	75
6	2.0	—	100	1.0	80
7	—	1.1	100	12	n.r.
8	—	—	100	12	n.r.
9	2.0	—	100	1.0	83
10	2.0	—	110	1.0	60
11	0.8	—	100	2.5	65
12	1.0	—	100	2.0	75
13	1.2	—	100	1.5	78
14	1.5	—	100	1.0	82 (86)[c]

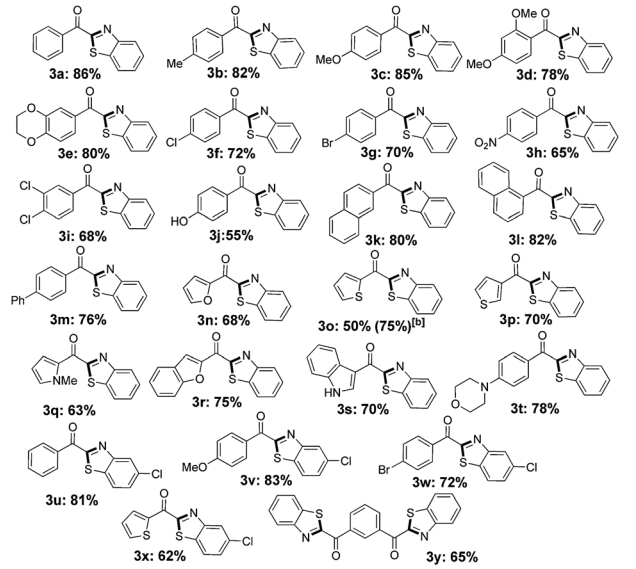
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol) in 3 mL DMSO. [b] Isolated yields. n.r. = no reaction. [c] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), in 3 mL DMSO.

Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, 430079, P. R. China. E-mail: chwuax@mail.ccnu.edu.cn; Fax: +86 027 6786 7773; Tel: +86 027 6786 7773

† Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for isolated compounds. See DOI: 10.1039/c2cc34561g

Table 2 The scope of aryl methyl ketones and *o*-aminobenzenethiols[a]



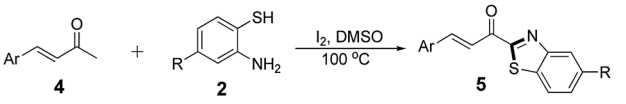


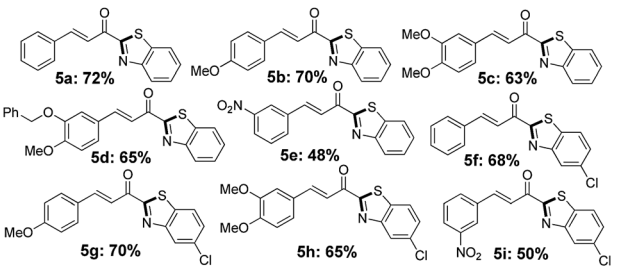
Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), I_2 (1.5 mmol) in DMSO (3 mL) at 100 °C for 1–2.5 h.[a] Isolated yield. [b] **1o** (1.0 mmol), **2a** (1.2 mmol), I_2 (1.5 mmol) in DMSO (3 mL) at 80 °C for 2.5 h.

With the optimal conditions in hand, the scope of the present transformation was investigated with I_2 as promoter. To our satisfaction, the reaction showed a wide scope for the structure of aromatic methyl ketones (Table 2). Both electron-donating and electron-withdrawing groups at the *ortho*-, *meta*- or *para*-position of the phenyl group of **1** could afford the corresponding products with moderate to good yields (**3a–3i**). It should be noted that an electron-donating substituent on the benzene ring caused a slight increase in yields. The substrate with a sensitive hydroxy group (OH) on the phenyl ring presented a moderate 55% yield of **3j**, whereas 1-naphthyl methyl ketone (**1k**) and 2-naphthyl methyl ketone (**1l**) afforded satisfying results (80% and 82% yields). Heteroaryl methyl ketones were also investigated. Heterocycles, including furanyl (**1n**), thiophenyl (**1o**, **1p**), *N*-methyl pyrrolyl (**1q**), benzofuryl (**1r**), 3-indolyl (**1s**) and morpholinyl (**1t**), were shown not to affect the overall efficiency, and the corresponding products **3n–3t** were obtained in moderate to good yields (63–78%). We were pleased to find 2-amino-4-chlorobenzenethiol (**2b**) was also tolerant to the reaction. The corresponding products **3u–3x** were thus obtained in 61–83% yields. Agreeably, dual substituted aromatic methyl ketone 1,1′-(1,3-phenylene)diethanone (**1y**) could also afford the corresponding product **3y** in 65% yield.

To further expand the scope of the ketones, unsaturated methyl ketones such as **4a–4e** were investigated. To our delight, unsaturated methyl ketones could also smoothly react with *o*-aminobenzenethiols **2** in the presence of I_2 to afford the corresponding products (Table 3). Electron donating groups attached to the aryl rings, such as MeO, benzyloxy, could

Table 3 The scope of unsaturated aryl methyl ketones and *o*-aminobenzenethiols[a]





Reaction conditions: **4** (1.0 mmol), **2** (1.2 mmol), I_2 (1.5 mmol) in DMSO (3 mL) at 100 °C for 1–2.5 h.[a] Isolated yield.

increase the yields (**5b–5d**, **5g–5h**), while an NO_2 group decreased the yields (**5e** and **5i**). The steric nature of the unsaturated methyl ketones had little influence on the reaction efficiency, and all the desired products were obtained in moderate to good yields (48–72%; Table 3). In addition, aliphatic ketones, such as acetone, cyclohexanone, and methylethylketone, were also investigated. However, none of the desired products were observed under the standard conditions.

The reaction process of **1a** (0.1 mmol), **2a** (0.12 mmol) with I_2 (0.12 mmol) was monitored by ^{1}H NMR spectroscopy. The experiment clearly illustrated that the reaction had a good conversion and yield. The consumption of **1a** was very fast at the first 15 mins (Fig. 1), and the formation of product **3a** was directly related to the consumption of **1a** (the integrals changed at δ = 2.57, 8.28, and 8.45 ppm). Moreover, we were delighted to find that a new species appeared at peak of 5.70–5.80 ppm, which was assigned to the byproduct HI of inner salt HI-**3a** *via* the ^{1}H NMR titration experiments of **3a** with HI (see ESI†).

To further probe the reaction process, we monitored the reaction of **1a** (0.1 mmol) with I_2 (0.12 mmol) by ^{1}H NMR spectroscopic studies (Fig. 2). Through comparison with an authentic sample (see ESI†), the signal at 4.6 ppm was

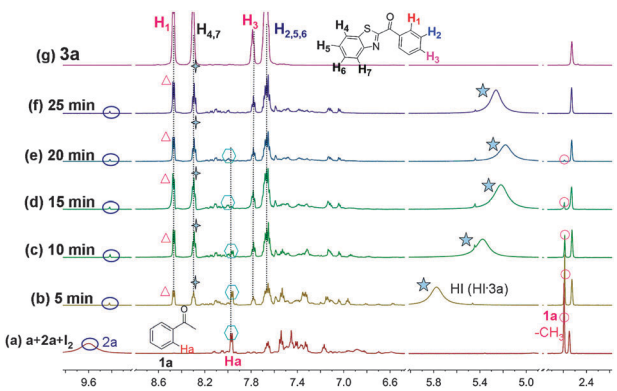


Fig. 1 The reaction process of **1a** (0.1 mmol) with **2a** (0.12 mmol) in the presence of I_2 (0.12 mmol) at 100 °C was monitored by ^{1}H NMR spectroscopy (600 MHz, DMSO-d_6, 298 +/−0.5 K).

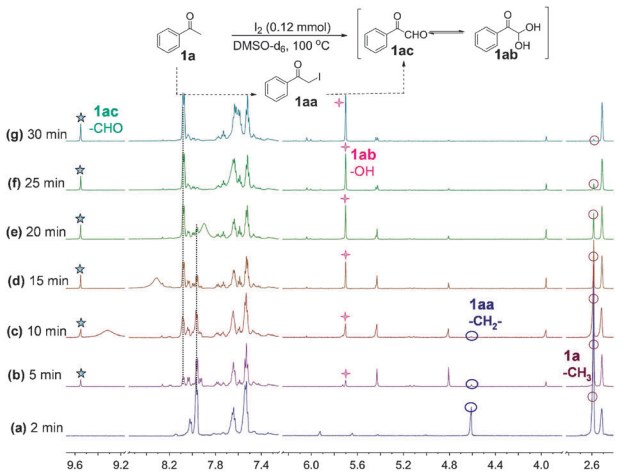
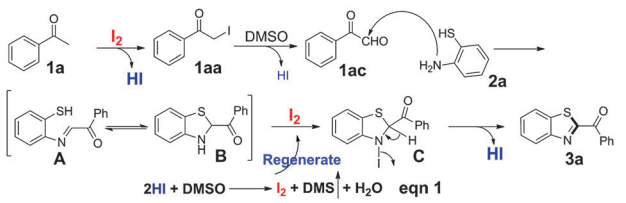


Fig. 2 The reaction process of **1a** (0.1 mmol) with I_2 (0.12 mmol) was monitored by ^{1}H NMR (600 MHz, DMSO-d_6, 298 +/−0.5 K) over time.



Scheme 1 The plausible mechanism of the present reaction.

assigned to the –CH_2– group of α-iodo aryl methyl ketone **1aa** at 2–10 mins (Fig. 2). In addition, the signals at 9.55 ppm and 5.70 ppm were assigned to the phenylglyoxal aldehyde group (**1ac**) and the hemiacetal group (**1ab**). With the consumption of **1a**, the intermediate **1ab** and **1ac** appeared and the concentration subsequently increased over time. Cocconcelli *et al*. had previously investigated the assignment and equilibrium between the aldehyde forms of phenylglyoxal **1ab** and the hydrated hemiacetal **1ac** *via* ^{1}H NMR spectra.[13] These results disclosed that phenacyl iodine (**1aa**) and phenylglyoxal (**1ac**) were important intermediates in the whole transformation.

A possible reaction mechanism is described as follows using acetophenone (**1a**) and 2-aminobenzenethiol (**2a**) as an example (Scheme 1). Initially, the acetophenone **1a** was converted to **1aa** in the media of I_2.[14] Subsequently, it further converted into phenylglyoxal (**1ac**) in the presence of DMSO.[15] Finally, phenylglyoxal (**1ac**) reacted with **2a** *via* condensation, Michael addition and oxidative dehydrogenation sequences to afford the desired product **3a** in the presence of the excess or regenerated iodide.[16] In the process, byproduct HI could be oxidized by DMSO to regenerate at least 0.5 equiv of iodine (eqn (1)).[17]

In conclusion, an I_2 promoted domino protocol has been developed to construct 2-acylbenzothiazoles from simple and readily available aromatic ketones/unsaturated methyl ketones and *o*-aminobenzenethiols. Mechanistic investigation disclosed that the transformation contained three mechanistically-different reactions (iodination, Kornblum oxidation, and heterocyclization). In addition, the protocol could provide a simple, efficient method to synthesize 2-acylbenzathiazoles, in which a metal, base, and ligand are needless. Further studies on the applications of this strategy will be reported in due course.

We thank the National Natural Science Foundation of China (Grant 21032001) and PCSIRT (No. IRT0953).

Notes and references

1 (*a*) C. G. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res*., 2001, **34**, 633; (*b*) F. Kakiuchi and S. Murai, *Acc. Chem. Res*., 2002, **34**, 826; (*c*) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (*d*) T. A. Ramirez, B. G. Zhao and Y. Shi, *Chem. Soc. Rev*., 2012, **41**, 931.
2 (*a*) M. Uyanik, H. Okamoto, T. Yasui and K. Ishihara, *Science*, 2010, **328**, 1376; (*b*) M. Uyanik, D. Suzuki, T. Yasui and K. Ishihara, *Angew. Chem., Int. Ed*., 2011, **50**, 5331; (*c*) M. Uyanik and K. Ishihara, *Chim. Oggi*, 2011, **29**, 18; (*d*) M. Uyanik and K. Ishihara, *ChemCatChem*, 2011, **4**, 177.
3 (*a*) T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner and B. J. Nachtsheim, *Org. Lett*., 2011, **13**, 3754; (*b*) U. Kloeckner, N. M. Weckenmann and B. J. Nachtsheim, *Synlett*, 2012, **23**, 97.
4 L. J. Ma, X. P. Wang, W. Yu and B. Han, *Chem. Commun*., 2011, **47**, 11333.
5 (*a*) W. Wei, C. Zhang, Y. Xu and X. B. Wan, *Chem. Commun*., 2011, **47**, 10827; (*b*) L. Chen, E. B. Shi, Z. J. Liu, S. L. Chen, W. Wei, H. Li, K. Xu and X. B. Wan, *Chem.–Eur. J*., 2011, **17**, 4085; (*c*) Z. J. Liu, J. Zhang, S. L. Chen, E. B. Shi, Y. Xu and X. B. Wan, *Angew. Chem., Int. Ed*., 2012, **51**, 3231; (*d*) E. B. Shi, Y. Shao, S. L. Chen, H. Y. Hu, Z. J. Liu, J. Zhang and X. B. Wan, *Org. Lett*., 2012, **14**, 3384.
6 J. Xie, H. L. Jiang, Y. X. Cheng and C. J. Zhu, *Chem. Commun*., 2012, **48**, 979.
7 (*a*) C. F. Wan, J. T. Zhang, S. J. Wang, J. M. Fan and Z. Y. Wang, *Org. Lett*., 2010, **12**, 2338; (*b*) J. T. Zhang, D. P. Zhu, C. M. Yu, C. F. Wan and Z. Y. Wang, *Org. Lett*., 2010, **12**, 2841; (*c*) C. F. Wan, L. F. Gao, Q. Wang, J. T. Zhang and Z. Y. Wang, *Org. Lett*., 2010, **12**, 3902; (*d*) Y. Z. Yang and Z. Y. Wang, *Chem. Commun*., 2011, **47**, 9513; (*e*) Q. Wang, C. F. Wan, Y. Gu, J. T. Zhang, L. F. Gao and Z. Y. Wang, *Green Chem*., 2011, **13**, 578.
8 H. F. Jiang, H. W. Huang, H. Cao and C. R. Qi, *Org. Lett*., 2010, **12**, 5561.
9 M. Lamani and K. R. Prabhu, *J. Org. Chem*., 2011, **76**, 7938.
10 X. B. Zhang and L. Wang, *Green Chem*., 2012, **14**, 2141.
11 (*a*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev*., 2003, **103**, 893; (*b*) K. Bahrami, M. M. Khodaei and F. Naali, *J. Org. Chem*., 2008, **73**, 6835.
12 (*a*) X. L. Yang, C. M. Xu, S. M. Lin, J. X. Chen, J. C. Ding, H. Y. Wu and W. K. Su, *J. Braz. Chem. Soc*., 2010, **21**, 37; (*b*) J. Hyvl and J. Srogl, *Eur. J. Org. Chem*., 2010, 2849; (*c*) X. S. Fan, Y. He, Y. Y. Wang, Z. K. Xue, X. Y. Zhang and J. J. Wang, *Tetrahedron Lett*., 2011, **52**, 899; (*d*) A. Shokrolahi, A. Zali and M. Mahdavi, *Phosphorus, Sulfur Silicon Relat. Elem*., 2012, **187**, 535.
13 V. Zuliani, G. Cocconclli, M. Fantini, C. Ghiron and M. Rivara, *J. Org. Chem*., 2007, **72**, 4551.
14 G. D. Yin, M. Gao, N. F. She, S. L. Hu, A.-X. Wu and Y. J. Pan, *Synthesis*, 2007, **20**, 3113.
15 (*a*) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand and W. M. Weaver, *J. Am. Chem. Soc*., 1957, **79**, 6562; (*b*) G. D. Yin, B. H. Zhou, X. G. Meng, A. X. Wu and Y. J. Pan, *Org. Lett*., 2006, **8**, 2245; (*c*) Y. P. Zhu, M. C. Liu, F. C. Jia, J. J. Yuan, M. Lian, Q. H. Gao and A. X. Wu, *Org. Lett*., 2012, **14**, 3392; (*d*) W. J. Xue, Q. Li, Y. P. Zhu, J. G. Wang and A. X. Wu, *Chem. Commun*., 2012, **48**, 3485.
16 M. Ishihara and H. Togo, *Synlett*, 2006, **2**, 227.
17 M. Gao, Y. Yang, Y. D. Wu, C. Deng, W. M. Shu, D. X. Zhang, L. P. Cao, N. F. She and A. X. Wu, *Org. Lett*., 2010, **12**, 4026.