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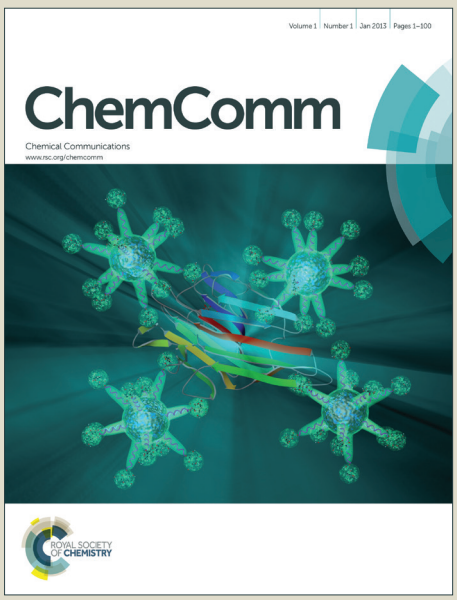

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Metal-free oxidative synthesis of quinazolinones via dual amination of sp^3 C–H bonds

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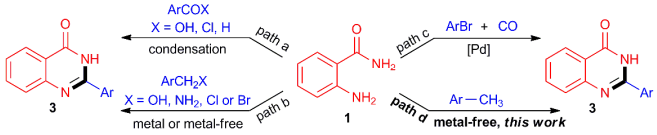
A novel metal-free synthesis of quinazolinones via dual amination of sp^3 C–H bonds was developed. The sp^3 carbon in methylarenes or adjacent to a heteroatom in DMSO, DMF or DMA was used as the one carbon synthon.

Quinazolinone heterocycle, widely presented in natural products and synthetic pharmaceuticals, has been extensively studied for its biological and therapeutic activities.[1] Many synthetic efforts have been made for its construction starting from a variety of substrates,[2] among which, 2-amino benzamide is probably the most typical one. Quinazolinones have commonly been prepared via condensation of 2-amino benzamides with either carboxylic acid derivatives under harsh conditions,[3] or aldehydes with subsequent oxidation using strong oxidants (Scheme 1, path a).[4] To overcome these drawbacks, recent reports gave improved methods using benzylic methylene sp^3 carbon as the one carbon synthon, developing a more environmentally friendly process (Scheme 1, path b). Benzyl alcohols were used for preparation of quinazolinones under metal or iodine catalytic systems.[5] Very recently, selective autoxidation of benzyl amines were also applied in this field, which possessed a highly valuable advantage.[6] Under Cu-catalyzed aerobic oxidative system, benzyl halides could be also served as starting materials.[7] Considering that carbon monoxide can be used as a cheap carbon source, palladium-catalyzed carbonylation reaction might become a promising strategy for heterocyclic compounds preparation. Very recently, an interesting work demonstrated that in the presence of a palladium catalyst, carbonylative synthesis of quinazolinones could be achieved starting from 2-amino benzamides and bromobenzenes (Scheme 1, path c).[8] Notably, all synthetic routes mentioned above depended on the use of functional group in substrate, which showed less atom-efficient compared with the attractive cross-dehydrogenative-coupling (CDC) reactions[9]. Besides, most of the cases were restricted to the transition metal assisted approach, which was a major problem regarding their practical applicability, especially in preparations of pharmaceutical agents due to the presence of heavy transition metal impurities in the final products. Therefore, a more environmentally friendly route for the synthesis of quinazolinones under metal-free conditions remains highly desirable.



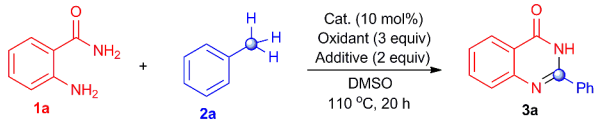
Scheme 1. Different pathways for the synthesis of quinazolinones.

In recent years, a great progress has been made in C–N bond formation via C–H/N–H cross-coupling but challenges still remained.[10] For example, methodologies for the amination of primary benzylic C–H bonds in toluene derivates are relatively scarce.[11] Notable examples included transition metal catalyzed,[11a,b] iodide salt catalyzed[11c] and hypervalent iodine mediated benzylic C–H amination via C–H/N–H cross-coupling,[11d,e] and the nitrogen sources were limited to sulphonamide, carboxamide and azole derivatives. Besides, there are few examples of the introduction of methylarenes or methylhetarenes to construct nitrogen-containing heterocycles via C–N bond formations.[12] Encouraged by above results, and in the continuation of our research on *N*-heterocycles,[13] we herein report a direct approach for the synthesis of quinazolinones from 2-amino benzamides and methylarenes (Scheme 1, path d). The transformation could be carried out via $(t\text{BuO})_2$ (DTBP) mediated domino reactions in which dual oxidative C–N couplings were involved, and quite different from the mentioned heterocycle construction reactions starting from methylarenes or methylhetarenes, transition metals were not essential.

Initially, as usual, transition metal catalysts were employed in the reaction of 2-amino benzamide (**1a**) and toluene (**2a**) in the presence of DTBP as oxidant (Table 1). As expected, the desired reaction took place, leading to the formation of the

product **3a** in moderate yield under iron or palladium catalysis (entries 1–3). To our surprise, a control experiment confirmed that the reaction occurred in the absence of the transition metal catalyst (entry 4). Interestingly, *p*-toluenesulfonic acid (TsOH) improved the yield significantly (entry 5). Among the various oxidants examined, we observed that DTBP was the most efficient one (entries 7–11). At this stage, other types of organic and inorganic acids were also tested, but not as efficient as TsOH (entries 12–18). The yields dropped after varying the amount of TsOH (entries 19–21), we deduced that TsOH could promote the reaction by adjusting the pH value of reaction solution.

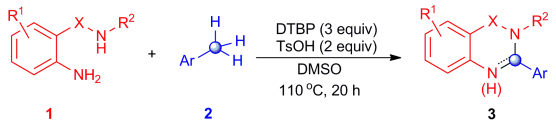
Table 1. Optimization of the reaction conditions[a]

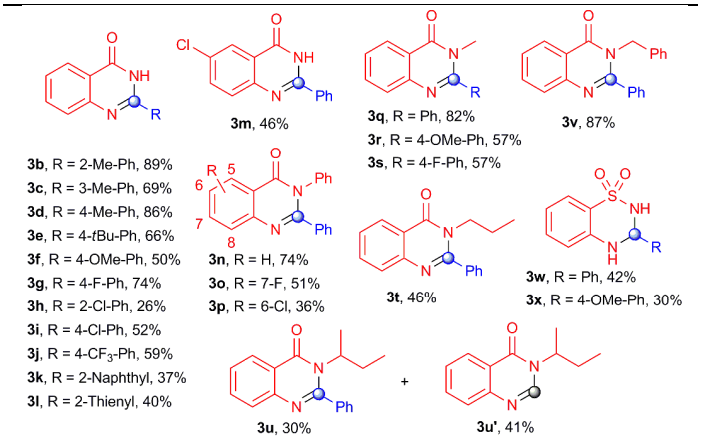


Entry	Cat.	Oxidant[b]	Additive	Yield[c] (%)
1	$FeCl_3$	DTBP	—	52
2	$CuCl_2$	DTBP	—	trace
3	$Pd(OAc)_2$	DTBP	—	57
4	—	DTBP	—	36
5	—	DTBP	TsOH	81
6	—	DTBP	K_2CO_3	trace
7	—	TBHP	TsOH	trace
8	—	BPO	TsOH	45
9	—	TBPB	TsOH	36
10	—	DDQ	TsOH	0
11	—	$K_2S_2O_8$	TsOH	0
12	—	DTBP	KH_2PO_4	16
13	—	DTBP	$BF_3{\cdot}Et_2O$	19
14	—	DTBP	CH_3COOH	31
15	—	DTBP	CF_3COOH	61
16	—	DTBP	*t*BuCOOH	57
17	—	DTBP	CH_3SO_3H	60
18	—	DTBP	CF_3SO_3H	42
19	—	DTBP	TsOH[d]	34
20	—	DTBP	TsOH[e]	73
21	—	DTBP	TsOH[f]	51

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (2 mL), cat. (10 mol%), oxidant (0.9 mmol), additive (0.6 mmol), DMSO (2 mL), 110 °C, 20 h. [b] TBHP: 70% *t*BuOOH in water, BPO: $(PhCOO)_2$, TBPB: PhCOO*t*Bu. [c] Isolated yield. [d] 0.5 equiv. [e] 1 equiv. [f] 3 equiv.

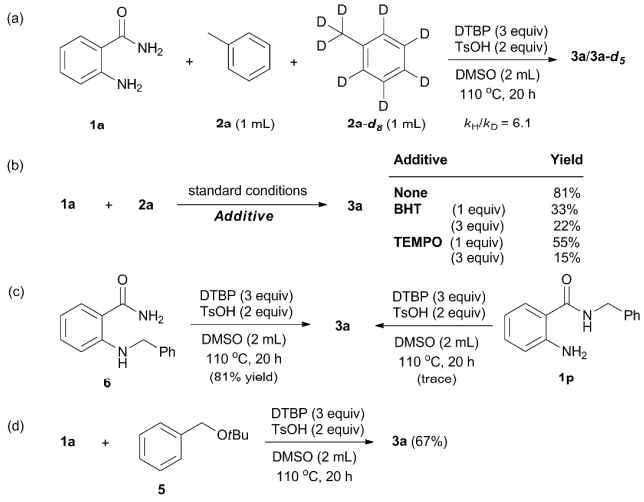
Table 2. Intermolecular annulation of **1** with methylarenes **2**[a]





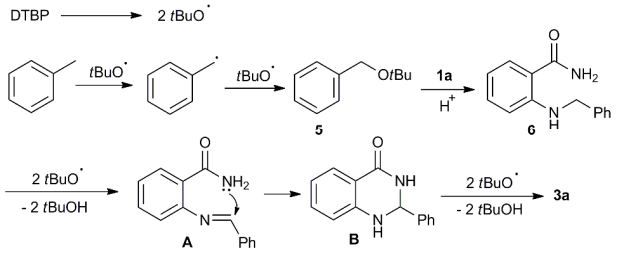
[a] Reaction conditions: **1** (0.3 mmol), **2** (2 mL), DTBP (0.9 mmol), TsOH (0.6 mmol), DMSO (2 mL), 110 °C, 20 h. Isolated yield.

Then, a wide range of 2-amino benzamides were employed for annulation with methylarenes under the optimized conditions (Table 2). Most of toluenes with electron-donating and withdrawing substituents could be converted to the desired products in moderate to good yields (**3b**–**j**). Remarkably, the steric hindrance had little influence on the reaction (**3b**–**d**). Methyl substituted naphthalene and heteroarene also proved applicable (**3k**–**l**). The substituents at the phenyl ring of 2-amino benzamides did not affect the efficiency of this transformation (**3m**, **3o**–**p**). This strategy was also available to the synthesis of quinazolinones bearing *N*-phenyl and *N*-alkyl substituents from corresponding 2-amino *N*-substituted benzamide with toluenes (**3n**–**v**). Surprisingly, when 2-amino-*N*-(*sec*-butyl)benzamide were subjected to identical conditions, the expected products **3u** was observed in 30% yield along with **3u'** in 41% yield. The low yield of **3u** was most probably attributed to steric effect of the *sec*-butyl group on the substrate. Moreover, a D-labeling experiment proved that the additional carbon atom in **3u'** was derived from DMSO (see ESI), which strongly suggested the methyl carbon of DMSO could be introduced as the one carbon synthon, although its reactivity was lower than that of toluene in current conditions. Because of the structural similarity, 2-amino benzenesulfonamide was tested and 3-phenyl-3,4-dihydro-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxides were obtained as products (**3w**–**x**). The yields were lower than those of quinazolinones, presumably due to the poorer nitrogen nucleophilicity of sulfonamides. Besides the intermolecular annulations using the above substrates, other potential substrates were tested (See ESI). We also tried intramolecular reaction to construct fused four-membered rings but failed (See ESI).



Scheme 2. Investigation into the reaction mechanism.

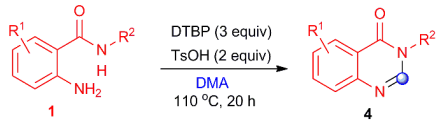
To obtain insights into the mechanism, some control experiments have been performed (Scheme 2). We first ruled out the possibility of benzaldehyde as the reaction intermediate and indeed didn't detect it in reaction mixture. The competitive annulations involving toluene and toluene-d_8 were performed, and a large intermolecular kinetic isotope effect (KIE, k_H/k_D = 6.1) was observed (Scheme 2a), thus indicating that the cleavage of benzyl C–H bond was involved in the rate-determining step. A negative influence on the yield was observed when BHT (2,6-di-*tert*-butyl-4-methylphenol) or TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) was added to the reaction system (Scheme 2b), which suggested that the reaction probably proceeded via a free radical process. We next investigated whether 2-(benzylamino)benzamide **6** or 2-amino *N*-benzylbenzamide **1p** was the reaction intermediate, and the results indicated that amino group instead of amide group played an important role in intermolecular amination (Scheme 2c). Considering that *tert*-butoxy intermediate was reported involved in C–N bond formation via nucleophilic reaction assisted by Lewis acid,[14] we speculated this intermediate could also be attacked by **1a** to give **6**, and subsequent intramolecular amination/oxidation would form the product **3a**. Expectedly, the reaction of **1a** and **5** afforded the product **3a** (Scheme 2d).



Scheme 3. Possible mechanism.

Therefore, a possible mechanism is proposed as shown in Scheme 3. Initially, the homolysis of DTBP gave *tert*-butoxy radicals.[15] Benzyl radical was then generated by abstraction of H from toluene, and subsequent coupling of these two radicals formed the intermediate **5**. Then **6** was generated from **5** via nucleophilic attack by **1a** in the presence of TsOH, followed by oxidation to give **A**. Subsequently, **A** was converted to annulation product **3a** via the second amination and followed oxidation.

Table 3. Intermolecular annulation of **1** with DMA[a]



4a, R = Ph, 72%
4b, R = 3-Me-Ph, 56%
4c, R = 4-Cl-Ph, 47%
4d, R = 4-OMe-Ph, 78%
4e, R = 1-Naphthyl, 61%
4f, R = 6-Me, 92%
4g, R = 7-F, 89%
4h, R = 6-Cl, 70%
4i, R = 6-Br, 72%
4j, R = 7-OMe, 30%
4k, R = Me, 63%[b]
4l, R = *n*Pr, 54%
4m (**3u'**), R = *s*Bu, 55%[c]
4n, R = CH_2Ph, 68%

[a] Reaction conditions: **1** (0.3 mmol), DTBP (0.9 mmol), TsOH (0.6 mmol), DMA (2 mL), 110 °C, 20 h. Isolated yield. [b] DMF (2 mL) instead of DMA was used. [c] DMSO (2 mL) instead of DMA was used.

After success in the elaboration of 2-substituted quinazolinones, we moved our focus back to investigating the possibility of DMSO as an efficient carbon source. Based on some related research,[16] we hypothesize that, nucleophilic attack of α-*tert*-butoxylated intermediate and a sequential C–S bond cleavage were involved, and the following domino process occurred similarly to those in Scheme 3. Then, further optimizations were carried out by testing the annulation of 2-amino-*N*-phenylbenzamide with similar sp^3 carbons adjacent to heteroatoms in some other solvents, and DMA was the best one considering the availability (see ESI). As described in Table 3, starting from substrates with *N*-aryl, *N*-alkyl or phenyl substituents, the desired products were obtained with moderate to excellent yields. Notably, functional groups such as F, Cl or Br remained intact, allowing for further functionalization of the products.

In conclusion, we have developed a novel, metal-free approach for the synthesis of 2-aryl quinazolinones via dual benzylic C–H bonds amination, using 2-amino benzamides and methylarenes as the accessible starting materials. The possible radical mechanistic pathway is also proposed on the basis of control experiments. In addition, the commonly used solvents, such as DMSO, DMF or DMA were also effective in the similar annulation reactions via sp^3 C–S or C–N bond cleavage and C–N bond formations. Further application of the methodology in other *N*-heterocycles synthesis is currently underway in our laboratory.

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Notes and references

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1. (*a*) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787; (*b*) A. Witt and J. Bergman, *Curr. Org. Chem.*, 2003, **7**, 659.
2. (*a*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893; (*b*) D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153; (*c*) L. He, H. Li, J. Chen and X.-F. Wu, *RSC Adv.*, 2014, **4**, 12065.

3. (*a*) A. V. Purandare, A. M. Gao, H. H. Wan, J. Somerville, C. Burke, C. Seachord, W. Vaccaro, J. Wityak and M. A. Poss, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2669; (*b*) T. M. Potewar, R. N. Nadaf, T. Daniel, R. J. Lahoti and K. V. Srinivasan, *Synth. Commun.*, 2005, **35**, 231.
4. (*a*) T. Hisano, M. Ichikawa, A. Nakagawa and M. Tsuji, *Chem. Pharm. Bull.*, 1975, **23**, 1910; (*b*) C. Balakumar, P. Lamba, D. P. Kishore, B. L. Narayana, K. V. Rao, K. Rajwinder, A. R. Rao, B. Shireesha and B. Narsaiah, *Eur. J. Med. Chem.*, 2010, **45**, 4904; (*c*) Y. Mitobe, S. Ito, T. Mizutani, T. Nagase, N. Sato and S. Tokita, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4075.
5. (*a*) J. Zhou and J. Fang, *J. Org. Chem.*, 2011, **76**, 7730; (*b*) H. Hikawa, Y. Ino, H. Suzuki and Y. Yokoyama, *J. Org. Chem.*, 2012, **77**, 7046; (*c*) A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *Org. Biomol. Chem.*, 2012, **10**, 240; (*d*) M. Sharif, J. Opalach, P. Langer, M. Beller and X.-F. Wu, *RSC Adv.*, 2014, **4**, 8; (*e*) D. Zhao, Y.-R. Zhou, Q. Shen and J.-X. Li, *RSC Adv.*, 2014, **4**, 6486; (*f*) W. Ge, X. Zhu and Y. Wei, *RSC Adv.*, 2013, **3**, 10817.
6. N. Thanh Binh, L. Ermolenko and A. Al-Mourabit, *Green Chem.*, 2013, **15**, 2713.
7. H. Wei, T. Li, Y. Zhou, L. Zhou and Q. Zeng, *Synthesis*, 2013, **45**, 3349.
8. X.-F. Wu, L. He, H. Neumann and M. Beller, *Chem.–Eur. J.*, 2013, **19**, 12635.
9. (*a*) C.-J. Li, *Acc. Chem. Res.*, 2008, **42**, 335; (*b*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215.
10. (*a*) F. Collet, C. Lescot and P. Dauban, *Chem. Soc. Rev.*, 2011, **40**, 1926; (*b*) F. Collet, R. H. Dodd and P. Dauban, *Chem. Commun.*, 2009, 5061; (*c*) D. N. Zalatan and J. Du Bois, *Top. Curr. Chem.*, 2010, **292**, 347.
11. For selected examples, see: (*a*) D. A. Powell and H. Fan, *J. Org. Chem.*, 2010, **75**, 2726; (*b*) Q. Xia, W. Chen and H. Qiu, *J. Org. Chem.*, 2011, **76**, 7577; (*c*) Q. Xue, J. Xie, H. Li, Y. Cheng and C. Zhu, *Chem. Commun.*, 2013, **49**, 3700; (*d*) H. J. Kim, J. Kim, S. H. Cho and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 16382; (*e*) R. Samanta, J. Lategahn and A. P. Antonchick, *Chem. Commun.*, 2012, **48**, 3194; (*f*) S. K.-Y. Leung, W.-M. Tsui, J.-S. Huang, C.-M. Che, J.-L. Liang and N. Zhu, *J. Am. Chem. Soc.*, 2005, **127**, 16629; (*g*) M. R. Fructos, S. Trofimenko, M. M. Díaz-Requejo and P. J. Pérez, *J. Am. Chem. Soc.*, 2006, **128**, 11784; (*h*) S. Wiese, Y. M. Badiei, R. T. Gephart, S. Mossin, M. S. Varonka, M. M. Melzer, K. Meyer, T. R. Cundari and T. H. Warren, *Angew. Chem., Int. Ed.*, 2010, **49**, 8850; (*i*) Z. Ni, Q. Zhang, T. Xiong, Y. Zheng, Y. Li, H. Zhang, J. Zhang and Q. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 1244; (*j*) Y. Amaoka, S. Kamijo, T. Hoshikawa and M. Inoue, *J. Org. Chem.*, 2012, **77**, 9959; (*k*) W. Xiao, J. Wei, C.-Y. Zhou and C.-M. Che, *Chem. Commun.*, 2013, **49**, 4619; (*l*) Y. M. Badiei, A. Dinescu, X. Dai, R. M. Palomino, F. W. Heinemann, T. R. Cundari and T. H. Warren, *Angew. Chem., Int. Ed.*, 2008, **47**, 9961; (*m*) R. T. Gephart, D. L. Huang, M. J. B. Aguila, G. Schmidt, A. Shahu and T. H. Warren, *Angew. Chem., Int. Ed.*, 2012, **51**, 6488; (*n*) K. Huard and H. Lebel, *Chem.–Eur. J.*, 2008, **14**, 6222.
12. (*a*) N. Thanh Binh, L. Ermolenko and A. Al-Mourabit, *J. Am. Chem. Soc.*, 2013, **135**, 118; (*b*) L. Gu, C. Jin, J. Guo, L. Zhang and W. Wang, *Chem. Commun.*, 2013, **49**, 10968.
13. (*a*) D. Zhao, M.-X. Zhu, Y. Wang, Q. Shen and J.-X. Li, *Org. Biomol. Chem.*, 2013, **11**, 6246; (*b*) D. Zhao, Q. Shen, Y.-R. Zhou and J.-X. Li, *Org. Biomol. Chem.*, 2013, **11**, 5908; (*c*) D. Zhao, T. Wang, Q. Shen and J.-X. Li, *Chem. Commun.*, 2014, **50**, 4302.
14. Q. Xia and W. Chen, *J. Org. Chem.*, 2012, **77**, 9366.
15. H. Yang, H. Yan, P. Sun, Y. Zhu, L. Lu, D. Liu, G. Rong and J. Mao, *Green Chem.*, 2013, **15**, 976.
16. (*a*) Y. Lv, Y. Li, T. Xiong, W. Pu, H. Zhang, K. Sun, Q. Liu and Q. Zhang, *Chem. Commun.*, 2013, **49**, 6439; (*b*) Y. Yan, Y. Zhang, C. Feng, Z. Zha and Z. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8077.

