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Synthesis of 2-C-substituted benzothiazoles *via* a copper-promoted domino condensation/S-arylation/heterocyclization process†

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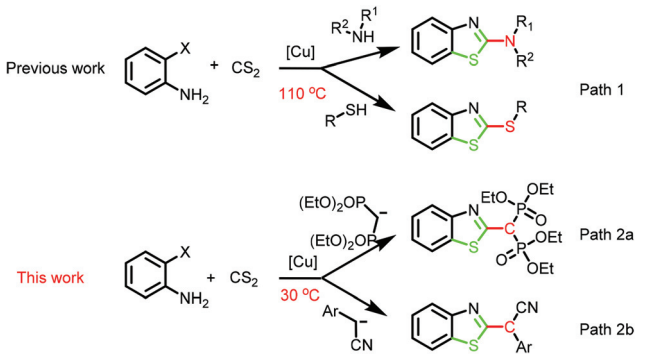
Two series of extremely useful 2-C-substituted benzothiazoles containing *gem*-bisphosphonates and aryl-substituted nitriles were synthesized here *via* a copper-promoted domino condensation/S-arylation/heterocyclization process.

Benzothiazole and its derivatives, a considerably important class of heterocycles, have drawn high attention because of their extensive application in the biological and pharmaceutical areas.[1] Particularly, 2-substituted benzothiazoles have been intensively studied on account of their various bioactivities, such as selective inhibitors of 17β-HSD1,[2] anti-fungal reagents,[3] antitumour agents[4] and the significant application of the core structure of benzothiazoles in clinical drugs.[5]

In light of the importance of the benzothiazole scaffold, considerable effort has been devoted to developing efficient synthetic approaches for this privileged structure. As is well-known, the normal methods reported before for the assembly of benzothiazole moieties typically rely on the condensation of 2-aminothiophenols with carboxylic acids or aldehydes, but such methods suffer from harsh reaction conditions and difficulties in the preparation of readily oxidized 2-aminothiophenols.[6] Additionally, many alternative methods to access benzothiazoles involving C–H functionalized cyclization of thiobenzanilide and transition metal-catalyzed intramolecular cyclization of 2-halophenyl benzothioamide have been reported.[7] However, these methods usually face considerable limitations, including low functional group tolerance since in most cases P_4S_{10} or Lawesson's reagent was used to prepare thioamide.[8] Thus the development of alternative and complementary methods for constructing the benzothiazole scaffold is highly desirable.

Recently, some alternative thiol reagents have been employed for the synthesis of benzothiazoles from conveniently available starting materials in one pot.[9] In 2009, Ma *et al.* reported an efficient method to access substituted benzothiazoles *via* a Cu-catalyzed coupling reaction of aryl halides with metal sulfides.[10] Successively, they developed novel synthetic methods to 2-S/N-substituted benzothiazoles using carbon disulfide as a thiol surrogate (Scheme 1, path 1).[9b,d] It was believed that dithiocarbamate salts were formed by treating amines/thiols with carbon disulfide, which might serve as novel coupling partners to react with 2-halo-anilines. Inspired by these developments, we speculated that a similar transformation would occur to provide 2-carbon-substituted benzothiazoles if nucleophiles were replaced with carbanions generated *in situ* in the presence of bases. Fortunately, after great efforts toward developing new methods for heterocycle synthesis, we found that nitrogen-containing bisphosphonates (N-BPs), 2-methylbisphosphonate-substituted benzothiazoles, and



Scheme 1 Synthetic approaches to two series of 2-C-substituted benzothiazoles.

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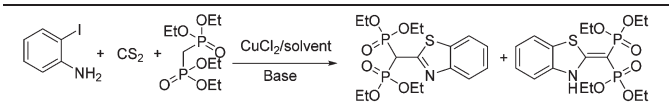
α-aryl-substituted nitriles, α-benzothiazol-substituted nitriles, could readily be obtained in our laboratory by employing bis(diethoxyphosphoryl)methanides and cyano(phenyl)methanides generated *in situ* respectively as nucleophiles instead of N and/or S nucleophiles in this cascade three-component reaction (Scheme 1, paths 2a and 2b). More importantly, this transformation is a significant complement to Ma's reaction.[9b,d]

As is well-known, nitrogen-containing bisphosphonates (N-BPs) are ubiquitous in numerous pharmaceuticals and agrochemicals owing to their broad range of biological activities, such as γ δ T cell stimulators,[11] anti-infective agents,[12] anti-cancer agents,[13] *etc*., especially as powerful inhibitors of bone resorption.[14] Moreover, in the clinic many N-BPs are currently applied widely to treat osteoporosis, Paget's disease and malignant hypercalcemia,[15] and these are the only clinically validated drugs targeting hFPPS.[16] In addition, α-aryl-substituted nitriles are also very valuable building blocks to gain amides, carboxylic acids, primary amines, ketones, heterocycles and biologically active compounds with or without the nitrile group.[17] Therefore, two series of quite useful 2-C-substituted benzothiazoles were synthesized here *via* a copper-catalyzed domino condensation/S-arylation/heterocyclization process.

Our present study commenced with the reaction of 2-iodoaniline **1a** with carbon disulfide and tetraethyl methylenebis(phosphonate) **2a** as a model to examine suitable reaction conditions (Table 1). Initially, previous optimized conditions (1.2 eq. CS_2, 3 eq. K_2CO_3, 1 eq. $CuCl_2$ in DMF at 110 °C for 6 h) reported by Ma's group[9d] were applied, but no desired product was detected (entry 1). Considering that carbanions might be unstable at high temperature, we lowered the temperature to 30 °C, but no reaction took place yet. We supposed that the base K_2CO_3 might not be strong enough to generate carbanions from methylenebis(phosphonate) **2a**, and thus a range of stronger bases were employed. To our delight, these stronger bases we screened excepting Cs_2CO_3 could provide the desirable products in moderate to good yields (entries 3–6). Among these bases, ^{t}BuOK turned out to be the best base with a 75% yield. Interestingly, the corresponding product **3a** was isolated as a tautomeric mixture with about 1 : 3 ratio of imine form **3a′** and enamine form **3a″** estimated by ^{1}H-NMR. As the next optimization step we performed a solvent screening (entries 7–10). None of the other solvents was superior to DMF. Obviously, nonpolar solvents led to considerably lower yields than polar solvents (entries 7, 8 *vs.* 6, 9, 10). After that, we finally surveyed the effect of temperature on the reaction, revealing that neither increasing nor lowering the reaction temperature gave higher yields compared to reacting at 30 °C.

With the optimized conditions (1.2 eq. CS_2, 3 eq. ^{t}BuOK, 1 eq. $CuCl_2$ in DMF at 30 °C for 12 h) in hand, a range of 2-halo-anilines were applied to explore the scope and limitations of this reaction (Table 2). We found that substrates **1** bearing electron-withdrawing and also electron-donating substituents

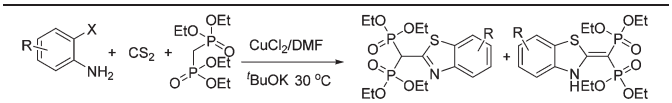
Table 1 Optimization of the reaction conditions[a]

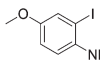
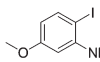


Entry	Base	Solvent	T [°C]	Yield[b,c] [%]
1	K_2CO_3	DMF	110	0
2	K_2CO_3	DMF	30	0
3	Cs_2CO_3	DMF	30	0
4	KOH	DMF	30	54
5	NaH	DMF	30	71
6	**^{t}BuOK**	**DMF**	**30**	**75**
7	^{t}BuOK	THF	30	<5
8	^{t}BuOK	Dioxane	30	<5
9	^{t}BuOK	DMSO	30	21
10	^{t}BuOK	NMP	30	51
11	^{t}BuOK	DMF	60	Trace
12	^{t}BuOK	DMF	10	Trace

[a] Reaction conditions: **1a** (0.25 mmol), CS_2 (0.3 mmol), **2a** (0.375 mmol), $CuCl_2$ (0.25 mmol), base (0.75 mmol), solvent (1 mL, anhydrous). [b] Isolated yield. [c] Ratio of imine form **3a′** and enamine form **3a″** was 1 : 3.

Table 2 Scope of 2-halo-anilines[a,c]



Entry	2-Halo-aniline	Product	Yield[b] (3′ : 3″)
1		**3a**	75% (1 : 3.3)
2		**3b**	73% (1 : 2.4)
3		**3c**	65% (1 : 4.0)
4		**3d**	45% (1 : 0.94)
5		**3e**	44% (1 : 2.3)
6		**3f**	61% (1 : 1.3)
7		**3g**	55% (1 : 1.8)
8		**3h**	48% (1 : 2.3)
9		**3b**	40% (1 : 2.4)

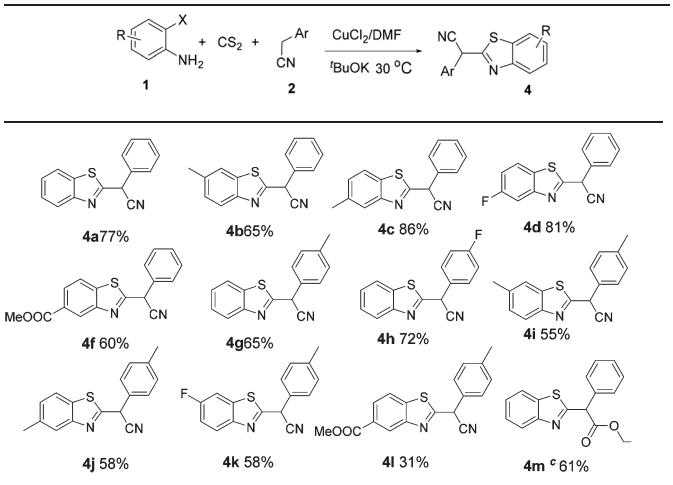
[a] Reaction conditions: **1** (0.25 mmol), CS_2 (0.3 mmol), **2** (0.375 mmol), $CuCl_2$ (0.25 mmol), ^{t}BuOK (0.75 mmol), solvent (1 mL, anhydrous). [b] Isolated yield. [c] The proportions of imine form **3′** and enamine form **3″** of compound **3** are given in parentheses.

on the benzene ring were tolerated. However, the yields of products were severely affected by the substituent's properties. It was also observed that weak electron-donating and electron-withdrawing substituents on compounds **1** such as –Me and –F gave similar or slightly lower yields than 2-iodoaniline without any substituent (entries 2, 3, 6, 7 *vs.* 1). When stronger electron-donating and electron-withdrawing substituents such as –OMe and –COOMe were introduced into the benzene ring, the expected products **3d–e** and **3h** were also obtained but in moderate yields (entries 4, 5, 8). To our delight, the desired product **3b** was also isolated in 40% yield when 2-iodoaniline was replaced by 2-bromoaniline (entry 9).

Inspired by the above results, we applied the same conditions to various commercially available phenylacetonitriles as another carbon nucleophile reagent. To our delight, when 2-iodoaniline was treated with phenylacetonitrile under standard conditions, α-benzothiazol-substituted nitrile **4a** was isolated in good yield. It is noteworthy that imine form **4a** was isolated exclusively compared to the N-BPs series. Without further optimization, various 2-iodoanilines and phenylacetonitriles were employed to extend the reaction scope, and thus another very useful series of 2-C-substituted benzothiazoles, α-benzothiazol-substituted nitriles, were obtained. As illustrated in Table 3, both electron-donating and electron-withdrawing substituents on the benzene ring of compounds **1** and **2** were well tolerated leading to the corresponding α-aryl-substituted nitrile products **4b–k** in moderate to good yields except product **4l** with an electron-donating group –Me and an electron-withdrawing group –COOMe on its substrates **1** and **2** respectively.

Finally, in order to extend the application of this methodology, we investigated other carbanion nucleophiles, diethyl malonate, malanonitrile, 1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione, diphenylmethane, ethynylbenzene and ethyl 2-phenylacetate. However, only ethyl 2-phenylacetate furnished the desired product **4m** with 61% yield (Table 3). The others we tried gave no desired products but with benzo[*d*]thiazole-2(3*H*)-thione as a byproduct, which have been mentioned in Ma's reaction.[9d]

Table 3 Reaction of various 2-halo-anilines with various phenylacetonitriles/ethyl 2-phenylacetate[a,b]



[a] Reaction conditions: **1a** (0.25 mmol), CS_2 (0.3 mmol), **2a** (0.375 mmol), $CuCl_2$ (0.25 mmol), ^{t}BuOK (0.75 mmol), solvent (1 mL, anhydrous). [b] Isolated yield. [c] Ethyl 2-phenylacetate was used instead of **2**.

In summary, a straightforward route to various 2-C-substituted benzothiazoles using 2-haloanilines as starting materials and carbon disulfide as a thiol surrogate was first developed by our group. Two series of medicinally useful 2-*gem*-bisphosphonate-substituted benzothiazoles and α-benzothiazol-substituted nitriles were synthesized here *via* a copper-promoted domino condensation/S-arylation/heterocyclization process. These synthetic 2-C-substituted benzothiazoles bearing cyano and bisphosphonate groups allow further formation of diverse medicinal derivatives.

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Notes and references

1 A. D. Weekes Aa Fau-Westwell and A. D. Westwell, *Curr. Med. Chem.*, 2009, **16**, 2430–2440.
2 A. Spadaro, M. Frotscher and R. W. Hartmann, *J. Med. Chem.*, 2012, **55**, 2469–2473.
3 Y. Liu, Y. Wang, G. Dong, Y. Zhang, S. Wu, Z. Miao, J. Yao, W. Zhang and C. Sheng, *Med. Chem. Commun.*, 2013, **4**, 1551.
4 (*a*) M. M. Stec, K. L. Andrews, S. K. Booker, S. Caenepeel, D. J. Freeman, J. Jiang, H. Liao, J. McCarter, E. L. Mullady, T. San Miguel, R. Subramanian, N. Tamayo, L. Wang, K. Yang, L. P. Zalameda, N. Zhang, P. E. Hughes and M. H. Norman, *J. Med. Chem.*, 2011, **54**, 5174–5184; (*b*) M. Okaniwa, M. Hirose, T. Arita, M. Yabuki, A. Nakamura, T. Takagi, T. Kawamoto, N. Uchiyama, A. Sumita, S. Tsutsumi, T. Tottori, Y. Inui, B. C. Sang, J. Yano, K. Aertgeerts, S. Yoshida and T. Ishikawa, *J. Med. Chem.*, 2013, **56**, 6478–6494.
5 B. L. Mylari, E. R. Larson, T. A. Beyer, W. J. Zembrowski, C. E. Aldinger, M. F. Dee, T. W. Siegel and D. H. Singleton, *J. Med. Chem.*, 1991, **34**, 108–122.
6 (*a*) Y. P. Zhu, M. Lian, F. C. Jia, M. C. Liu, J. J. Yuan, Q. H. Gao and A. X. Wu, *Chem. Commun.*, 2012, **48**, 9086–9088; (*b*) X. Fan, Y. He, Y. Wang, Z. Xue, X. Zhang and J. Wang, *Tetrahedron Lett.*, 2011, **52**, 899–902; (*c*) Y. F. Liao, H. R. Qi, S. P. Chen, P. C. Jiang, W. Zhou and G. J. Deng, *Org. Lett.*, 2012, **14**, 6004–6007.
7 (*a*) X.-J. Mu, J.-P. Zou, R.-S. Zeng and J.-C. Wu, *Tetrahedron Lett.*, 2005, **46**, 4345–4347; (*b*) K. Inamoto, C. Hasegawa, K. Hiroya and T. Doi, *Org. Lett.*, 2008, **10**, 5147–5150; (*c*) K. Inamoto, C. Hasegawa, J. Kawasaki, K. Hiroya and

T. Doi, *Adv. Synth. Catal.*, 2010, **352**, 2643–2655; (*d*) K. Inamoto, K. Nozawa and Y. Kondo, *Synlett*, 2012, 1678–1682.

8 Y. D. Sun, H. F. Jiang, W. Q. Wu, W. Zeng and X. Wu, *Org. Lett.*, 2013, **15**, 1598–1601.

9 (*a*) D. J. Prasad and G. Sekar, *Org. Biomol. Chem.*, 2013, **11**, 1659–1665; (*b*) L. Shi, X. Liu, H. Zhang, Y. Jiang and D. Ma, *J. Org. Chem.*, 2011, **76**, 4200–4204; (*c*) W. J. Xue, Y. Q. Guo, F. F. Gao, H. Z. Li and A. X. Wu, *Org. Lett.*, 2013, **15**, 890–893; (*d*) D. Ma, X. Lu, L. Shi, H. Zhang, Y. Jiang and X. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 1118–1121.

10 D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong and Y. Jiang, *Angew. Chem., Int. Ed.*, 2009, **48**, 4222–4225.

11 Y. Zhang, R. Cao, F. Yin, F. Y. Lin, H. Wang, K. Krysiak, J. H. No, D. Mukkamala, K. Houlihan, J. Li, C. T. Morita and E. Oldfield, *Angew. Chem., Int. Ed.*, 2010, **49**, 1136–1138.

12 A. P. Singh, Y. Zhang, J. H. No, R. Docampo, V. Nussenzweig and E. Oldfield, *Antimicrob. Agents Chemother.*, 2010, **54**, 2987–2993.

13 Y. Zhang, R. Cao, F. Yin, M. P. Hudock, R.-T. Guo, K. Krysiak, S. Mukherjee, Y.-G. Gao, H. Robinson, Y. Song, J. H. No, K. Bergan, A. Leon, L. Cass, A. Goddard, T.-K. Chang, F.-Y. Lin, E. V. Beek, S. Papapoulos, A. H. J. Wang, T. Kubo, M. Ochi, D. Mukkamala and E. Oldfield, *J. Am. Chem. Soc.*, 2009, **131**, 5153–5162.

14 A. Balakrishna, M. V. Narayana Reddy, P. V. Rao, M. A. Kumar, B. S. Kumar, S. K. Nayak and C. S. Reddy, *Eur. J. Med. Chem.*, 2011, **46**, 1798–1802.

15 (*a*) A. A. Reszka and G. A. Rodan, *Mini. Rev. Med. Chem.*, 2004, **4**, 711–719; (*b*) K. Ohgi, H. Kajiya, F. Okamoto, Y. Nagaoka, T. Onitsuka, A. Nagai, R. Sakagami and K. Okabe, *Naunyn–Schmiedeberg's Arch. Pharmacol.*, 2013, **386**, 589–598; (*c*) Y. Zhang, A. Leon, Y. Song, D. Studer, C. Haase, L. A. Koscielski and E. Oldfield, *J. Med. Chem.*, 2006, **49**, 5804–5814.

16 Y.-S. Lin, J. Park, J. W. De Schutter, X. F. Huang, A. M. Berghuis, M. Sebag and Y. S. Tsantrizos, *J. Med. Chem.*, 2012, **55**, 3201–3215.

17 J. S. You and J. G. Verkade, *J. Org. Chem.*, 2003, **68**, 8003–8007.

