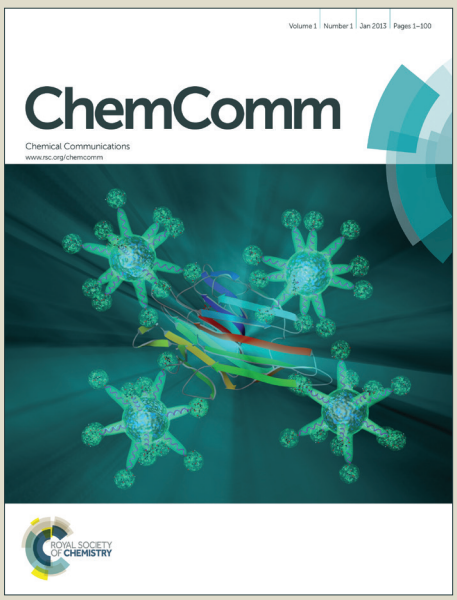
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Synthesis of naphthalene amino esters and arylnaphthalene lactone lignans through tandem reactions of 2-alkynylbenzonitriles

Yan He, Xinying Zhang, and Xuesen Fan*

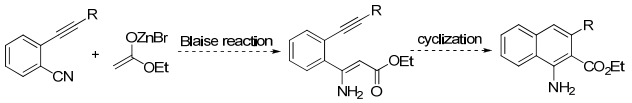
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Tandem reaction of 2-alkynylbenzonitriles with Reformatsky reagent turned out to be a novel and efficient approach toward 1-aminonaphthalene-2-carboxylates. Interestingly, with 2-(3-hydroxyprop-1-ynyl)benzonitriles as the substrates, a more sophisticated cascade process occurred to give 9-aminonaphtho[2,3-*c*]furan-1(3*H*)-ones in good yields. By using this tandem reaction as a key step, a concise and versatile synthetic strategy for the total synthesis of arylnaphthalene lactone lignans has been developed.

Functionalized naphthalenes, frequently found in natural products, pharmaceuticals and electronic materials,[1-2] were traditionally synthesized by stepwise introduction of required functional groups onto the naphthalene core *via* electrophilic substitutions.[3] However, the applicability of this strategy is compromised owing to limited availability of suitable naphthalene substrates and difficulty in controlling the regio-selectivity. To circumvent these limitations, synthesis of substituted naphthalenes from readily available benzene precursors turned out to be an attractive alternative.[4-6] Following this strategy, an efficient synthesis of 1-amino-2-naphthalene carboxylic acids *via* reacting 2-(α-lithioalkyl) benzonitriles with α,β-unsaturated carboxylates or nitriles has been developed by Kobayashi.[7] More recently, Sudalai revealed a novel preparation of naphthalene amino esters through CuCN-mediated one-pot cyclization of 4-(2-bromo phenyl)-2-butenoates.[8] While these elegant processes are generally efficient and reliable, a motivation to develop more practical and convenient approaches carried out under mild conditions still strongly persists.

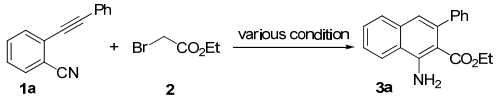
Recently, zinc enolates have found broad applications due to their versatile reactivity and excellent functional group tolerance.[9] As demonstrated by Lee[10], Johnson[11] and others, addition of Reformatsky reagent onto carbonyl or cyano group to form new enolates or zinc bromide complex of β-enamino ester and elaboration of these versatile intermediates have emerged as a powerful tool in the preparation of a plethora of compounds. Inspired by these pioneering achivements, we envisioned a new synthesis of 1-aminonaphthalene-2-carboxy-lates *via* a cascade procedure combining a zinc-mediated Blaise reaction of 2-alkynylbenzonitriles and subsequent intramolecular cyclization of the *in situ* formed enamine intermediates (Scheme 1).



Scheme 1 Proposed synthesis of functionalized naphthalene.

Thus, 2-(phenylethynyl)benzonitrile (**1a**) was prepared *via* Sonogashira coupling of 2-bromobenzonitrile with ethynyl benzene and then treated with ethyl 2-bromoacetate (**2**, 1 equiv.) and zinc powder (1 equiv.) in THF at 80 ºC for 2 h. To our delight, the reaction gave the desired ethyl 1-amino-2-naphthoate (**3a**) in a yield of 45% (Table 1, entry 1). To optimize the reaction conditions, CH_3CN, DCE and DMF were studied as alternative solvents. It turned out that they were less effective than THF in mediating this cascade process (entries 2-4). Next, the effect of the quantity of **2** and zinc was investigated (entries 5-8). Promisingly, when 2 equiv. of **2** and 3 equiv. of zinc were used, the yield of **3a** raised to 75% and the time period for a complete conversion shortened to 0.5 h (entry 7). Nevertheless, further increase in the quantity of **2** and zinc did not improve the reaction obviously (entry 8). It was also found that when the reaction was run at lower temperatures, the yield of **3a** decreased dramatically (entries 9-10). It was noted herein the intermediate aminoester as shown in Scheme 1 was not obtained or observed.

Table 1 Optimization studies for the formation of **3a**[a]



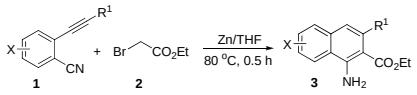
1a **2** **3a**

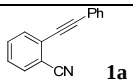
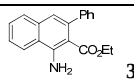
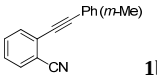
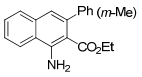
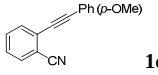
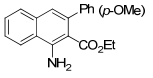
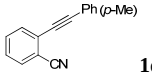
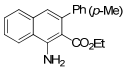
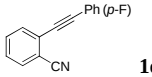
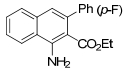
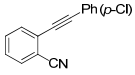
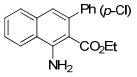
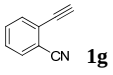
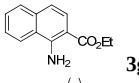
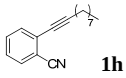
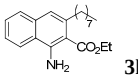
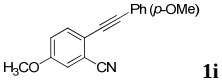
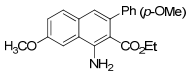
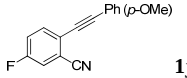
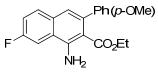
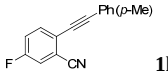
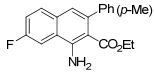
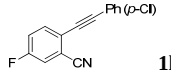
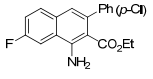
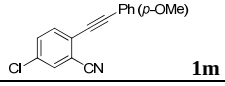
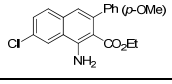
Entry	**2** (eq.)	zinc (eq.)	T (°C)	Solvent	t (h)	Yield (%)[b]
1	1	1	80	THF	2	45
2	1	1	80	CH_3CN	2	20
3	1	1	80	DCE	2	15
4	1	1	80	DMF	2	trace
5	1	2	80	THF	1	50
6	1	3	80	THF	1	56
7	**2**	**3**	**80**	**THF**	**0.5**	**75**
8	3	4	80	THF	0.5	76
9	2	3	r.t.	THF	2	trace
10	2	3	60	THF	2	55

[a] Reaction conditions: **1a** (0.5 mmol), solvent (2 mL); [b] Isolated yield.

With the optimized conditions (Table 1, entry 7), a range of 2-alkynylbenzonitriles (**1**) were screened to probe the scope of this reaction. The results listed in Table 2 showed that all the substrates reacted smoothly with ethyl 2-bromoacetate (**2**) and zinc to furnish the corresponding 1-aminonaphthalene-2-carboxylates (**3**) in good to excellent yields and various functional groups were well tolerable. It was noted that while the X unit in **1** could be hydrogen, methoxy, fluoro or chloro, substrates with a fluoro or chloro group (**1j-1m**) gave relatively higher yields. As for the scope of R^1, it could be not only an aryl unit (**1a-1f**, **1i-1m**), but also a hydrogen (**1g**) or an alkyl (**1h**) group. These results indicates that this synthetic method is suitable for the preparation of naphthalene with diverse substitution patterns. It was notable that in all cases only the 6-endo pathway was observed and the 5-exo-dig product was not found.

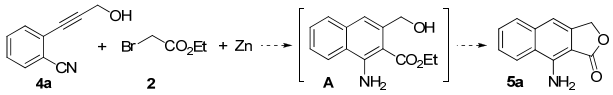
Table 2 Scope of the reaction leading to **3**[a]



Entry	Substrates (**1**)	Products (**3**)	Yield (%)[b]
1	 **1a**	 **3a**	75
2	 **1b**	 **3b**	73
3	 **1c**	 **3c**	69
4	 **1d**	 **3d**	71
5	 **1e**	 **3e**	77
6	 **1f**	 **3f**	75
7	 **1g**	 **3g**	68
8	 **1h**	 **3h**	65
9	 **1i**	 **3i**	68
10	 **1j**	 **3j**	84
11	 **1k**	 **3k**	83
12	 **1l**	 **3l**	86
13	 **1m**	 **3m**	88

[a] Reaction conditions: 1 mmol of **1**, 2 mmol of **2**, 3 mmol of zinc, 3 mL of THF, 80 °C, 0.5 h; [b] Isolated yield.

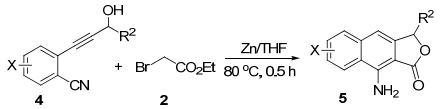
In further exploration on the scope of substrates, we postulated that if 2-(3-hydroxyprop-1-ynyl)benzonitrile (**4a**) was used to replace **1a**, the *in situ* formed 1-amino-3-(hydroxylmethyl)-2-naphthoate (**A**) *via* Blaise reaction of **4a** may simultaneously undergo a lactonization to give 9-amino naphtho[2,3-*c*]furan-1(3*H*)-one (**5a**, Scheme 2).[12]

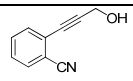
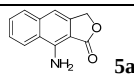
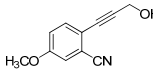
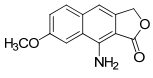
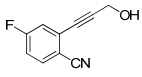
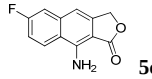
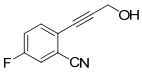
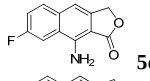
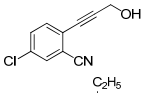
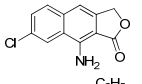
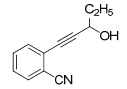


Scheme 2 Proposed one-pot formation of **5a** from **4a**

Indeed, treatment of **4a** with **2** and zinc in THF at 80 ºC afforded **5a** in a yield of 70%. Further studies showed that this cascade process was suitable for a wide range of substrates possessing either EWG or EDG (X) on the benzene moiety. In addition, both alkyl (Table 3, entries 6-7) and phenyl (entries 8-10) substituted 3-hydroxyprop-1-ynyl unit participated in this tandem reaction as smoothly as that without a substituent (entries 1-5) to afford the corresponding products with good efficiency, and this thus results in a simple and general synthetic protocol toward naphtho[2,3-*c*]furan-1(3*H*)-ones.[13]

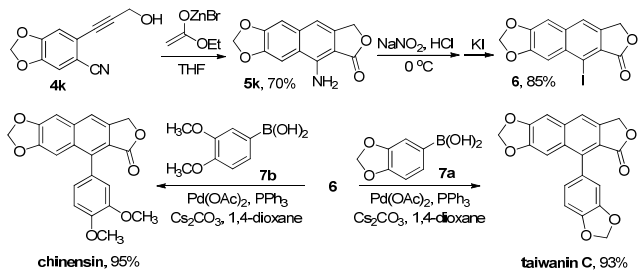
Table 3 Scope of the reaction leading to **5**[a]



Entry	Substrates (**4**)	Products (**5**)	Yield (%)[b]
1	 **4a**	 **5a**	70
2	 **4b**	 **5b**	62
3	 **4c**	 **5c**	77
4	 **4d**	 **5d**	75
5	 **4e**	 **5e**	78
6	 **4f**	**5f**	72
7	**4g**	**5g**	66
8	**4h**	**5h**	82
9	**4i**	**5i**	74
10	**4j**	**5j**	88

[a] Reaction conditions: 1 mmol of **4** , 2 mmol of **2**, 3 mmol of Zn, 3 mL of THF, 80 ºC, 0.5 h; [b] Isolated yield.

It is well known that arylnaphthalene lactone lignans are plant derived natural products with a wide range of valuable medicinal properties and therefore have been of continued interest in drug discovery.[14] It is also noticed that 9-amino naphtho[2,3-*c*]furan-1(3*H*)-one (**5**) has the same naphthalene lactone scaffold as that in arylnaphthalene lactone lignans and the amino group embeded in **5** is actually a convenient intermediary for the introduction of an aryl unit. On the basis of these observations, we were then interested in developing a new strategy for the total synthesis of arylnaphthalene lactone natural products by using the synthetic protocol developed above as a key step. Thus, 6-(3-hydroxyprop-1-ynyl)benzo [*d*][1,3]dioxole-5-carbonitrile (**4k**) was reacted with **2** and zinc to afford 9-amino-6,7-methylenedioxynaphtho[2,3-*c*] furan-1(3*H*)-one (**5k**). Treatment of **5k** with aqueous solution of hydrochloric acid and sodium nitrite followed by addition of potassium iodide gave 9-iodo-6,7-methylenedioxynaphtho [2,3-*c*]furan-1(3*H*)-one (**6**). Suzuki coupling of **6** with the commercially available benzo[*d*][1,3]dioxol-5-yl boronic acid (**7a**) afforded tawanin C (Scheme 3). Similarly, coupling of **6** with 3,4-dimethoxyphenyl boronic acid (**7b**) afforded another member of the arylnaphthalene lactone family, chinensin. Given the broad scope of **4** and **7**, this concise and versatile strategy should be able to provide numerous arylnaphthalene lactone lignans with diverse substitution patterns, which is extremely important for drug discovery in which a large number of related compounds with diverse functional groups are needed for biological activity screening.



Scheme 3 Total synthesis of tawanin C and chinensin.

In summary, we have revealed efficient and convenient syntheses of 1-aminonaphthalene-2-carboxylates and 9-amino naphtho[2,3-*c*]furan-1(3*H*)-ones *via* Blaise reaction of 2-alkynylbenzonitriles followed by 6-π cyclization and lactonization. More interestingly, 9-aminonaphtho[2,3-*c*]furan-1(3*H*)-ones were found to be convenient intermediates to arylnaphthalene lactone lignans. As a result, a concise and versatile strategy for the total synthesis of naturally occurring arylnaphthalene lactones, chinensin and taiwanin C, was developed. Studies to find more applications of zinc mediated cascade reactions are currently underway in our lab and the results will be reported in due course.

We are grateful to the National Natural Science Foundation of China (21172057, 21272058), RFDP (20114104110005), PCSIRT (IRT1061) and 2012IRTSTHN006 for financial support.

Notes and references

[a] *School of Chemistry and Chemical Engineering, School of Environment, Collaborative Innovation Centre of Henan Province for Green Manufacturing of Fine Chemicals, Henan Key Laboratory for Environmental Pollution Control, Henan Normal University, Xinxiang, Henan 453007, P. R. China. E-mail: xuesen.fan@htu.cn*

† Electronic Supplementary Information (ESI) available: Experimental procedures, characterisation data and NMR spectra. See DOI: 10.1039/ b000000x/

1 (*a*) R. S. Ward, *Nat. Prod. Rep*., 1995, **12**, 183; (*b*) R. S. Ward, *Nat. Prod. Rep*., 1997, **14**, 43; (*c*) R. S. Ward, *Nat. Prod. Rep*., 1999, **16**, 75; (*d*) T. Ukita, Y. Nakamura, A. Kubo, Y. Yamamoto, M. Takahashi, J. Kotera and T. Ikeo, *J. Med. Chem.,* 1999, **42**, 1293; (*e*) O. Silva and E. T. Gomes, *J. Nat. Prod.,* 2003, **66**, 447; (*f*) J. Dai, Y. Liu, Y.-D. Zhou and D. G. Nagle, *J. Nat. Prod.,* 2007, **70**, 1824; (*g*) K. Krohn, S. F. Kounam, S. Cludius-Brandt, S. Draeger and B. Schulz, *Eur. J. Org. Chem.,* 2008, 3615.

2 M. D. Watson, A. Fechtenkotter and K. Mullen, *Chem Rev*., 2001, **101**, 1267.

3 R. Norman and J. M. Coxon, *Principles of Organic Synthesis*, 3rd ed.; Chapman & Hall, Inc.: New York, 1993; p 355.

4 (*a*) A. Asao, K. Takahashi, S. Lee, T. Kasahara and Y. Yamamoto, *J. Am. Chem. Soc.,* 2002, **124**, 12650; (*b*) A. Asao, T. Nogami, S. Lee and Y. Yamamoto, *J. Am. Chem. Soc.,* 2003, **125**, 10921.

5 (*a*) R. Balamurugan and V. Gudla, *Org. Lett.,* 2009, **11**, 3116; (*b*) A. S. Dudnik, T. Schwier and V. Gevorgyan, *Org. Lett.,* 2008, **10**, 1465.

6 (*a*) M. Shimizu, Y. Tomioka, L. Nagao, T. Kadowaki and T. Hiyama, *Chem. Asian J.,* 2012, **7**, 1644; (*b*) F. Yang, T. Jin, M. Bao and Y. Yamamoto, *Chem. Commun.,* 2011, **47**, 4013.

7 K. Kobayashi, T. Uneda, K. Takada, H. Tanaka, T. Kitamura, O. Morikawa and H. Konishi, *J. Org. Chem.,* 1997, **62**, 664.

8 R. S. Reddy, P. K. Prasad, B. B. Ahuja and A. Sudalai, *J. Org. Chem.,* 2013, **78**, 5045.

9 T. Hama, S. Ge and J. F. Hartwig, *J. Org. Chem*., 2013, **78**, 8250 and references cited therein.

10 (*a*) Y. S. Chun, K. K. Lee, Y. O. Ko, H. Shin and S.-g. Lee, *Chem. Commun.,* 2008, 5098; (*b*) Y. O. Ko, Y. S. Chun, C.-L. Park, Y. Kim, H. Shin, S. Ahn, J. Hong and S.-g. Lee, *Org. Biomol. Chem.,* 2009, **7**, 1132; (*c*) Y. S. Chun, Y. O. Ko, H. Shin and S.-g. Lee, *Org. Lett.,* 2009, **11**, 3414; (*d*) Y. S. Chun, K. Y. Ryu, Y. O. Ko, J. Y. Hong, J. Hong, H. Shin and S.-g. Lee, *J. Org. Chem.,* 2009, **74**, 7556; (*e*) Y. S. Chun, K. Y. Ryu, J. H. Kim, H. Shin and S.-g Lee, *Org. Biomol. Chem.,* 2011, **9**, 1317; (*f*) J. H. Kim and S.-g. Lee, *Org. Lett.,* 2011, **13**, 1350; (*g*) Y. S. Chun, J. H. Lee, J. H. Kim, Y. O. Ko, and S.-g. Lee, *Org. Lett.,* 2011, **13**, 6390.

11 (*a*) S. N. Greszler and J. S. Johnson, *Angew. Chem., Int. Ed.,* 2009, **48**, 3689; (*b*) S. N. Greszler, J. T. Malinowski and J. S. Johnson, *J. Am. Chem. Soc.,* 2010, **132**, 17393.

12 For the biological significance of butenolide derivatives, see: (*a*) B. C. B. Bezuidenhoudt, A. Swanepoel, E. V. Brandt and D. Ferreira, *J. Chem. Soc., Perkin Trans. 1,* 1990, 2599; (*b*) J. K. Son, D. H. Kim and M. H. Woo, *J. Nat. Prod.,* 2003, **66**, 1369; (*c*) J. Dogné, C. T. Supuran and D. Pratico, *J. Med. Chem.,* 2005, **48**, 2251; (*d*) E. E. Shults, J. Velder, H.-G. Schmalz, S. V. Chernov, T. V. Rubalava, Y. V. Gatilov, G. Henze, G. A. Tolstikov and A. Prokop, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 4228 and references cited therein; (*e*) L. Tu, Y. Zhao, Z. Yu, Y. Cong, G. Xu, L. Peng, P. Zhang, X. Cheng and Q. Zhao, *Helv. Chim. Acta,* 2008, **91**, 1578.

13 For the synthesis of naphtho[2,3-*c*]furan-1(3*H*)-ones, see: (*a*) K. Kobayashi, J. Tokimatsu, K. Maeda, O. Morikawa and H. Konishi, *J. Chem. Soc. Perkin Trans. 1*, 1995, 3013; (*b*) S. H. Bergens, D. P. Fairlie and B. Bosnich, *Organometallics,* 1990, **9**, 566.

14 (*a*) P. Foley, N. Eghbali and P. T. Anastas, *J. Nat. Prod.*, 2010, **73**, 811; (*b*) V. Gudla and R. Balamurugan, *J. Org. Chem*., 2011, **76**, 9919 and references cited therein.