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Synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid ethyl esters from arylmethyl azides *via* a domino process†

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A convenient synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid ethyl esters *via* a domino process is described. The synthesis employs arylmethyl azides as the precursor which undergoes an acid-promoted rearrangement to give an *N*-aryl iminium ion. Following the addition with ethyl 3-ethoxyacrylate, intramolecular electrophilic aromatic substitution, elimination and subsequent oxidation, the quinoline products were obtained in moderate to excellent yields.

The quinoline ring system constitutes an important structural scaffold in various natural products which reveal numerous biologically significant properties such as antimicrobial,[1] anti-TB,[2] anticancer,[3] anti-HIV,[4] and antimalarial activities.[5] The quinoline skeleton is often an attractive framework to be used in the design of several synthetic compounds against diverse pharmacological targets leading to discovery of new drugs. Therefore, many methods for the synthesis of quinolines[6] have been developed including Combes quinoline synthesis,[7] Conrad–Limpach synthesis,[8] Friedlander synthesis,[9] Camps quinoline synthesis,[7c] Knorr quinoline synthesis,[10] Skraup synthesis,[11] Niementowski quinoline synthesis,[12] Povarov reaction,[13] Gould–Jacobs reaction,[14] and Doebner–Miller reaction.[15]

In particular, 2,4-unsubstituted quinoline-3-carboxylate derivatives have recently received much interest from pharmaceutical industries as this core structure is present in many agents under development to become commercial drugs, some of which are exemplified in Fig. 1.[16]

However, practical ways to synthesize this crucial core structure (**3**) are rare in the literature. The currently available methods require a long multi-step synthesis, long reaction time, high temperature and expensive starting materials (Scheme 1).[17] To improve the preparation of these compounds (**3**), factors such as commercial availability of substrates possessing wide structural variety as well as the ease of preparation of these substrates, when they are not commercially available, must be considered. These are important in evaluating the practicality and efficiency of these synthetic methods. Recently, Venkatesan and co-workers have reported a convenient and efficient one-step procedure for the synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid ethyl ester **3** from *o*-nitrobenzaldehydes (**5**) and 3,3-diethoxypropionic acid ethyl ester (**6**) in the presence of $SnCl_2{\cdot}2H_2O$ under refluxing

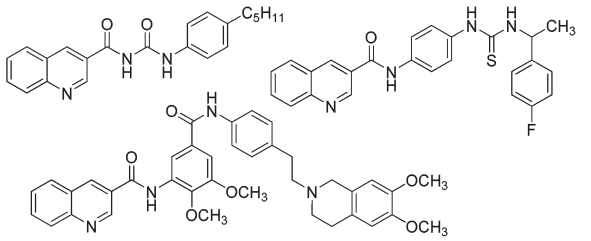
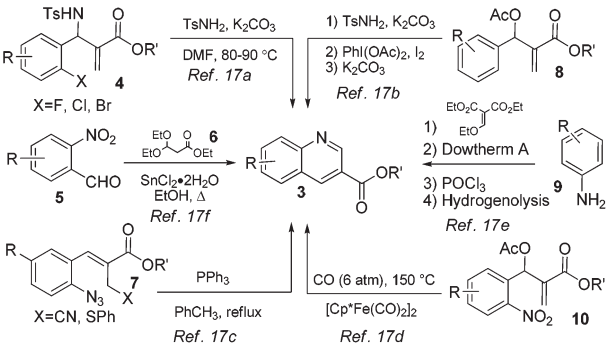


Fig. 1 Examples of pharmaceutical interest containing a 2,4-unsubstituted quinoline-3-carboxylate skeleton.



Scheme 1 Synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid ethyl ester **3**.

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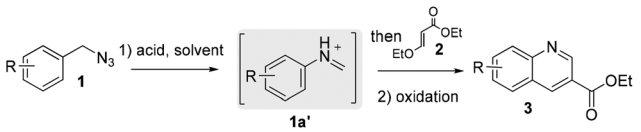
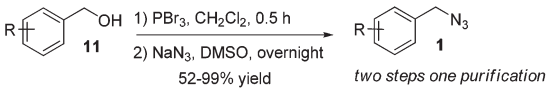
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ob27493d



Scheme 2 Synthetic strategy for the synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid ethyl ester **3**.



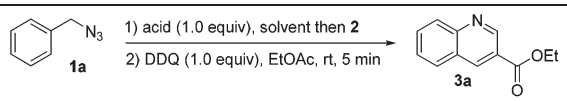
Scheme 3 Synthesis of arylmethyl azide derivatives.

conditions.[17f] However, this method does not allow for adequate diversity and substitution on the quinoline ring system **3** due to the limited number of commercially available *o*-nitrobenzaldehyde derivatives, some of which are expensive. Moreover, *o*-nitrobenzaldehyde derivatives are difficult to obtain by most processes.[18]

Our research group has been investigating the azide rearrangement reactions that deliver the *N*-aryl iminium ion intermediate **1a′** which can be trapped with a variety of nucleophiles.[19] Relating to this chemistry, we envision that 2,4-unsubstituted quinoline-3-carboxylic acid ethyl ester **3** could be generated by nucleophilic addition of ethyl 3-ethoxyacrylate (**2**) to the iminium ion followed by intramolecular electrophilic aromatic substitution and oxidation, constituting a domino process,[20] as shown in Scheme 2.

To search for the optimal conditions for our proposed quinoline synthesis, we used benzyl azide (**1a**) as our substrate for optimization. Based on earlier work both by our group and others,[19] TfOH and $TiCl_4$ are most optimal to effect the rearrangement of arylmethyl azides in either dichloromethane (DCM) or toluene. Therefore, we first investigated the rearrangement–cyclization sequence using 1.0 equiv. of TfOH and 1.0 equiv. of ethoxyacrylate **2** in DCM, which only provided 24% of the desired quinoline after oxidation with 1.0 equiv. of DDQ (entry 1, Table 1). We then switched to toluene and found that yield could be slightly improved to 38%. We next increased the amount of the acrylate to 2.0 equiv. while keeping everything else unchanged and found that yields in both solvents improved significantly, although toluene was still superior. Moreover, we found that the yield of the desired quinoline product improved from 67% to 79% (entry 5) when the reaction time was decreased. From these results, we speculated that the desired quinoline product may have been decomposed under these strongly acidic conditions in prolonged reaction time. We also attempted the reaction in toluene at 0 °C and observed a complex reaction mixture. Additionally, we attempted the reaction in toluene and THF using $TiCl_4$ and obtained only starting material unreacted (entries 7 and 8). The reaction in toluene in the presence of 2.0 equiv. of ethyl 3-ethoxyacrylate (**2**) and 1.0 equiv. of TfOH at room temperature was chosen as the general method.

Table 1 Optimization of the synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid ethyl ester **3a**



Entry	Acids	Solvent	Equiv. (2)	Time (h)	Yield[a] (%)
1	TfOH	CH_2Cl_2	1.0	12	24
2	TfOH	Toluene	1.0	12	38
3	TfOH	CH_2Cl_2	2.0	12	57
4	TfOH	Toluene	2.0	12	67
5	TfOH	Toluene	2.0	3	79
6[b]	TfOH	Toluene	2.0	3	40
7	$TiCl_4$	Toluene	2.0	12	NR
8	$TiCl_4$	THF	2.0	12	NR

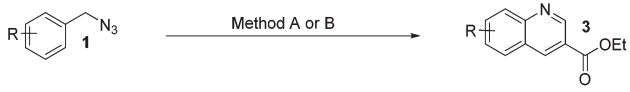
[a] Isolated total yield over 2 steps. [b] The reaction was carried out at 0 °C to room temperature.

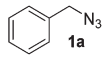
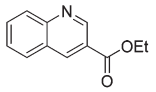
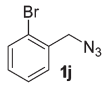
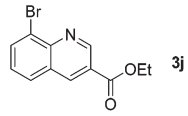
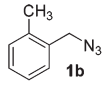
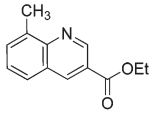
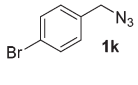
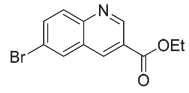
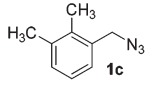
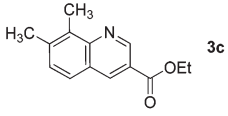
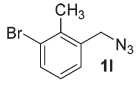
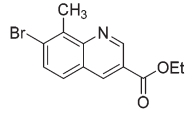
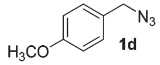
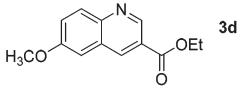
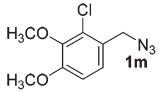
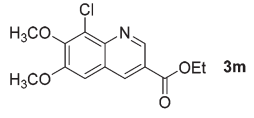
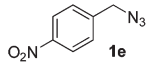
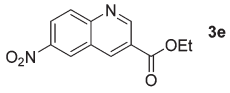
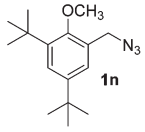
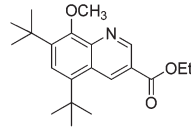
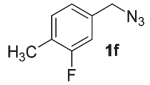
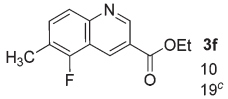
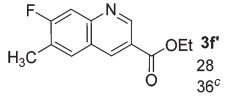
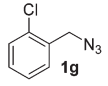
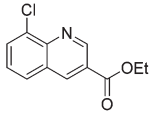
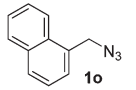
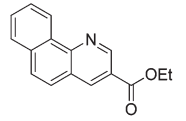
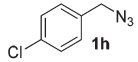
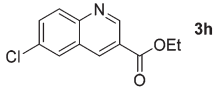
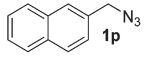
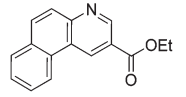
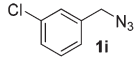
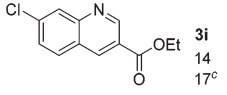
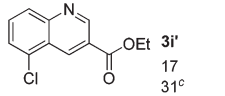
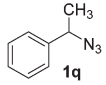
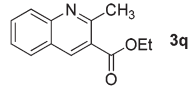
We then applied these optimal conditions to a variety of arylmethyl azide substrates to verify the generality of the method. Various arylmethyl azide substrates can be prepared in two steps in good to excellent yields from the corresponding arylmethyl alcohols **11** as shown in Scheme 3.[21]

As summarized in Table 2, the reactions proceeded readily with *o*-tolylmethyl azide (**1b**) and 2,3-xylylmethyl azide (**1c**) to give the desired quinolines **3b** and **3c** in 76% and 83% yields, respectively. When the aromatic ring was substituted with an electron-donating group (entry 4), the quinoline product **3d** was obtained in only 24% yield. The reaction of nitro-substituted benzyl azide **1e** furnished the product **3e** in lower yield (14%). We also attempted the reaction with *m*-fluorobenzyl azide (**1f**) and *m*-chlorobenzyl azide (**1i**) and obtained a mixture of regioisomeric products in both cases; 10% and 28% yields (entry 6), and 17% and 14% yields (entry 9), respectively. Moreover, the effects of halobenzyl azide derivatives with different substitution patterns were explored (entries 7–8 and 10–11). For *o*-chlorobenzyl azide (**1g**), the quinoline product was obtained in 54% yield. For *p*-chlorobenzyl azide (**1h**), the reaction provided a mixture of the quinoline product **3h** and the uncyclized by-product **16** (R═Cl) which could not be separated. However based on ^{1}H-NMR analysis of the purified products, the yield of the quinoline product was determined to be *ca.* 71% (Method A). Bromine substitution was also tolerated in this reaction (**1j** and **1k**). For *p*-bromobenzyl azide (**1k**), upon purification the reaction also provided an inseparable mixture of the quinoline **3k** and the uncyclized by-product **16** (R═Br); the yield of **3k** was determined to be *ca.* 78% based on ^{1}H-NMR analysis (Method A). Substrates with more complexity also provided the desired quinoline products in moderate to good yields (entries 12–16). However, when the secondary arylmethyl azide **1q** was employed (entry 17), only a trace amount of the desired 2-methyl quinoline product **3q** was observed by ^{1}H-NMR in the complex reaction mixture.

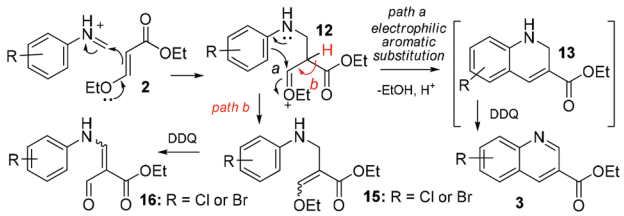
The reaction mechanism of this process is proposed as illustrated in Scheme 4. An acid-promoted rearrangement of arylmethyl azide for the generation of an *N*-aryl iminium ion serves as a key step. The iminium ion formed reacted with **2** to

Table 2 Optimization of the synthesis of 2,4-unsubstituted-3-carbalkoxy quinolines **3**



Entry	Substrate	Product	Yield[a] (%)	Entry	Substrate	Product	Yield[a] (%)
1	 **1a**	 **3a**	79	10	 **1j**	 **3j**	70
2	 **1b**	 **3b**	76 55[c]	11	 **1k**	 **3k**	53[b] 56[c]
3	 **1c**	 **3c**	83 55[c]	12	 **1l**	 **3l**	77 59[c]
4	 **1d**	 **3d**	24	13	 **1m**	 **3m**	53
5	 **1e**	 **3e**	14	14	 **1n**	 **3n**	70
6	 **1f**	 **3f** 10 19[c]	 **3f'** 28 36[c]				
7	 **1g**	 **3g**	54	15	 **1o**	 **3o**	56
8	 **1h**	 **3h**	36[b] 56[c]	16	 **1p**	 **3p**	64
9	 **1i**	 **3i** 14 17[c]	 **3i'** 17 31[c]	17	 **1q**	 **3q**	Trace

[a] Method A: (1) benzylic azide (1.0 equiv.), TfOH (1.0 equiv.), toluene, rt, 3 h, then **2** (2.0 equiv.); (2) DDQ (1.0 equiv.), EtOAc, rt, 5 min. [b] The reaction was carried out according to Method A, except after 2 h at rt the reaction was heated to 90 °C for 1 h. [c] Method B: (1) benzylic azide (1.1 equiv.), TfOH (1.1 equiv.), toluene, rt, then $BF_3{\cdot}OEt_2$ (1.0 equiv.), then **2** (1.0 equiv.).



Scheme 4 Proposed reaction mechanism.

generate the oxonium ion intermediate **12**. This intermediate can either undergo intramolecular electrophilic aromatic substitution and elimination of ethanol to afford the presumably dihydroquinoline intermediate **13** which was not isolable[22] and was directly oxidized with DDQ to yield the desired quinoline product **3** (*path a*) or undergo elimination to obtain ethoxyacrylate **15** (R═Br) which could be isolated. Upon oxidation of **15** (R═Br) with DDQ, uncyclized by-product **16** (R═Br) was obtained (*path b*).

The results showed that the competition between the formation of the desired quinoline product **3** (*path a*) and uncyclized by-products **16** (*path b*) depended on the reactivity of the aromatic ring. To suppress the formation of these by-products, we tried to heat the reaction mixture to 90 °C; while the by-products were not observed after heating, unfortunately the yields of the desired quinolines (**3h** and **3k**) dropped to 36% and 53%, respectively. We speculated that the ethoxyacrylate **2** could act as a proton acceptor which may cause *path b* to be more favorable when the aromatic ring was not reactive enough to cyclize. Therefore, we decided to make compound **2** the limiting agent and used 1.1 equiv. of benzylic azide (entries 8 and 11). We then tried several Lewis acids to promote the cyclization step and found that $BF_3{\cdot}OEt_2$ (Method B)[23] could increase the yields of **3h** and **3k** to 56% in both cases (compared to 36% and 53%, see above) and no uncyclized by-products were observed. However, this method provided the quinoline products in lower yields compared to Method A. We also applied Method B to benzylic azides in entries 2, 3, 6, 9 and 12. Yields of the desired quinoline products were moderate, however, yields of products in entries 6 and 9 were significantly higher compared to Method A.

Conclusions

In conclusion, we have developed a new method for the synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid ethyl esters **3** *via* a domino process starting from arylmethyl azide derivatives **1** and ethyl 3-ethoxyacrylate (**2**) in two synthetic steps and requiring only one purification. The current synthetic method can be conveniently conducted on a wide variety of the azide substrates. In addition, $BF_3{\cdot}OEt_2$ could be used to promote the same process which required less amount of acrylate **2**.

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Notes and references

1 (*a*) S. Sabatini, F. Gosetto, G. Manfroni, O. Tabarrini, G. W. Kaatz, D. Patel and V. Cecchetti, *J. Med. Chem.*, 2011, **54**, 5722–5736; (*b*) R. Nandhakumar, T. Suresh, A. L. C. Jude, V. R. Kannan and P. S. Mohan, *Eur. J. Med. Chem.*, 2007, **42**, 1128–1136; (*c*) A. H. Kategaonkar, P. V. Shinde, A. H. Kategaonhar, S. K. Pasale, B. B. Shingate and M. S. Shingare, *Eur. J. Med. Chem.*, 2010, **45**, 3142–3146.

2 A. Lilienkampf, J. Mao, B. Wan, Y. Wang, S. G. Franzblau and A. P. Kozikowski, *J. Med. Chem.*, 2009, **52**, 2109–2118.

3 Y.-W. Chen, Y.-L. Chen, C.-H. Tseng, C.-C. Liang, C.-N. Yang, Y.-C. Yao, P.-J. Lu and C.-C. Tzeng, *J. Med. Chem.*, 2011, **54**, 4446–4461.

4 J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 166–187.

5 (*a*) F. Bellot, F. Coslédéric, L. Vendier, J. Brocard, B. Meunier and A. Robert, *J. Med. Chem.*, 2010, **53**, 4103–4109; (*b*) R. Klingenstein, P. Melnyk, S. R. Leliveld, A. Ryckebusch and C. Korth, *J. Med. Chem.*, 2006, **49**, 5300–5308; (*c*) V. K. Zishiri, M. C. Joshi, R. Hunter, K. Chibale, P. J. Smith, R. L. Summers, R. E. Martin and T. J. Egan, *J. Med. Chem.*, 2011, **54**, 6959–6968.

6 P. E. Alford, in *Progress in Heterocyclic Chemistry*, ed. G. W. Gribble and J. A. Joule, Elsevier, Ltd., Oxford, 2011, vol. 23, pp. 349–358.

7 (*a*) E. C. Franklin and F. W. Bergstrom, *Chem. Rev.*, 1944, **35**, 77–277; (*b*) J. L. Born, *J. Org. Chem.*, 1972, **37**, 3952–3953; (*c*) R. H. Manske, *Chem. Rev.*, 1942, **30**, 113–144.

8 (*a*) R. H. Reitsema, *Chem. Rev.*, 1948, **43**, 43–68; (*b*) G. A. Reynolds and C. R. Hauser, in *Organic Syntheses*, ed. C. S. Hamilton, John Wiley & Sons, 1949, vol. 29, p. 70.

9 (*a*) P. G. Dormer, K. K. Eng, R. N. Farr, G. H. Humphrey, J. C. McWilliams, P. J. Reider, J. W. Sager and R. P. Volante, *J. Org. Chem.*, 2003, **68**, 467–477; (*b*) S. S. Palimkar, S. A. Siddiqui, T. Daniel, R. J. Lahoti and K. V. Srinivasan, *J. Org. Chem.*, 2003, **68**, 9371–9378; (*c*) R. Martínez, D. J. Ramón and M. Yus, *J. Org. Chem.*, 2008, **73**, 9778–9780.

10 (*a*) C. R. Hauser and G. A. Reynolds, *J. Am. Chem. Soc.*, 1948, **70**, 2402–2404; (*b*) A. J. Jodgkinson and B. Staskun, *J. Org. Chem.*, 1969, **34**, 1709–1713.

11 (*a*) R. H. F. Manske and M. Kulka, *Org. React.*, 1953, **7**, 59–98; (*b*) H. T. Clarke and A. W. Davis, in *Organic*

Synthesis, ed. J. B. Conant, John Wiley & Sons, 1922, vol. 2, p. 79.

12 R. J. Chongau, M. A. Siddiqui and V. Snieckus, *Tetrahedron Lett.*, 1986, **27**, 5323–5326.

13 (*a*) H. Twin and R. A. Batey, *Org. Lett.*, 2004, **6**, 4913–4916; (*b*) H. Richter and O. G. Mancheño, *Org. Lett.*, 2011, **13**, 6066–6069; (*c*) M. J. Bouma, G. Masson and J. Zhu, *Eur. J. Org. Chem.*, 2012, 475–479.

14 R. G. Gould and W. A. Jacobs, *J. Am. Chem. Soc.*, 1939, **61**, 2890–2895.

15 (*a*) M. Matsugi, F. Tabusa and J.-I. Minamikawa, *Tetrahedron Lett.*, 2000, **41**, 8523–8525; (*b*) J. J. Eisch and T. Dluzniewski, *J. Org. Chem.*, 1989, **54**, 1269–1276.

16 (*a*) P. Weikop, M. B. Nielsen, L. S. Madsen and C. Mathisen, *Patent WO* 2008/31831 A2, 2008; (*b*) J. Mitchell and H. Fields, *Patent US* 2006/258647 A1, 2006; (*c*) A. Phadke, D. Chen, M. Meshpande, A. Thurkauf, X. Wang, Y. Shen, C. Liu, J. Quinn, J. Ohkanda and S. Li, *Patent US* 2006/25416 A1, 2006; (*d*) J. D. Bloom, K. J. Curran, M. J. Digrand, R. G. Dushin, S. A. Lang, E. B. Norton, A. A. Ross and B. M. O'Hara, *Patent EP* 1137645 B1, 2004.

17 (*a*) J. N. Kim, H. J. Lee, K. Y. Lee and H. S. Kim, *Tetrahedron Lett.*, 2001, **42**, 3737–3740; (*b*) J. N. Kim, Y. M. Chung and Y. J. Im, *Tetrahedron Lett.*, 2002, **43**, 6209–6211; (*c*) H. J. Kim, E. M. Jeong and K.-J. Lee, *J. Heterocycl. Chem.*, 2011, **48**, 965–972; (*d*) D. K. O'Dell and K. M. Nicholas, *J. Org. Chem.*, 2003, **68**, 6427–6430; (*e*) R. E. Lutz, C. J. Ohnmacht, Jr. and F. Davis, *J. Med. Chem.*, 1971, **14**, 17–24; (*f*) H. Venkatesan, F. M. Hocutt, T. K. Jones and M. H. Rabinowitz, *J. Org. Chem.*, 2010, **75**, 3488–3491.

18 (*a*) C. I. Sainz-Diaz and A. Hernandez-Laguna, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1489–1495; (*b*) C. I. Sainz-Diaz, *Monatsh. Chem.*, 2002, **133**, 9–22; (*c*) W. Ertel, *US Patent US* 4297519, 1991; (*d*) W. Meyer, *US Patent US* 4203928, 1980.

19 (*a*) J. Tummatorn, C. Thongsornkleeb and S. Ruchirawat, *Tetrahedron*, 2012, **68**, 4732–4739; (*b*) W. H. Pearson and W.-K. Fang, *Isr. J. Chem.*, 1997, 37–39; (*c*) P. Desai, K. Schildknegt, K. A. Agrios, C. Mossman, G. L. Milligan and J. Aubé, *J. Am. Chem. Soc.*, 2000, **122**, 7226–7232; (*d*) Z. Song, Y.-M. Zhao and H. Zhai, *Org. Lett.*, 2011, **13**, 6331–6333.

20 L. F. Tietze, G. Brasche and K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley VCH, Weinheim, Germany, 2006.

21 Safety precaution should be taken seriously when preparing benzylic azides. Dichloromethane from the first step should be removed completely to avoid the formation of diazidomethane when using NaN_3 in the next step. See: R. E. Conrow and W. D. Dean, *Org. Process Res. Dev.*, 2008, **12**, 1285–1286.

22 We attempted to isolate this intermediate, however the intermediate decomposed on silica gel during purification.

23 See ESI† for optimization of Method B.