Facile synthesis of 3-(aminomethyl)isoquinolines by copper-catalysed domino four-component coupling and cyclisation†

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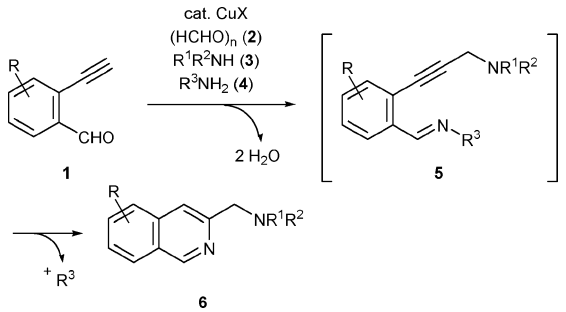
Received (in Cambridge, UK) 26th November 2007, Accepted 12th December 2007
First published as an Advance Article on the web 4th January 2008
DOI: 10.1039/b718201e

Copper(I)-catalysed domino four-component coupling–cyclisation using 2-ethynylbenzaldehydes, paraformaldehyde, secondary amine, and *t*-BuNH$_2$ in DMF leads to direct and efficient formation of 3-(aminomethyl)isoquinolines in good to high yields.

The isoquinoline scaffold can be found in a wide variety of biologically active natural and synthetic compounds.[1] Particularly, isoquinolines having an additional nitrogen atom tethered by one carbon at the 3-position, including such isoquinoline alkaloids as quinocarcin[2] and ecteinascidin 597 and 583,[3] and 3-(2-pyridinyl)isoquinolines,[4] constitute an important class of compounds with important biological activities. With a continuing interest in the development of environmentally-benign synthesis as well as multi-component reactions in modern synthetic chemistry,[5] we planned a novel diversity-oriented synthetic methodology for the construction of these molecules by the use of a domino multi-component coupling–cyclisation reaction.

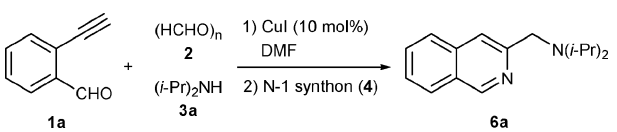
Recently, we have reported an efficient construction of 2-(aminomethyl)indoles by a copper-catalysed three-component coupling–cyclisation reaction.[6] This reaction proceeds through Mannich-type coupling followed by indole formation. On the basis of our indole synthesis, we expected that a four-component coupling reaction of 2-ethynylbenzaldehydes **1**, aldehyde **2**, secondary amine **3**, and an appropriate N-1 synthon **4**, followed by cyclisation of the alkyne intermediate **5**, having a nitrogen atom in proximity to the triple bond,[7,8] would provide a direct route to 3-(aminomethyl)isoquinolines **6** without wasting any salts (Scheme 1). Herein, we describe a copper-catalysed domino four-component coupling–cyclisation reaction for diversity-oriented synthesis of 3-(aminomethyl)isoquinolines. To the best of our knowledge, this is the first example of a four-component synthesis of an isoquinoline scaffold.[9]

In the initial investigation, we examined the effect of the N-1 synthon on the copper-catalysed four-component synthesis of 3-(aminomethyl)isoquinoline using 2-ethynylbenzaldehyde **1a** as a model substrate, paraformaldehyde **2** and diisopropylamine **3a** (Table 1). Since two nucleophilic reagents coexist with two aldehydes in the reaction system, progress of the nucleophilic reactions in the desired order might be hampered on one-portion reaction.[10] Accordingly, after the copper-catalysed three component reaction of **1a**, **2**, and **3a** in DMF was complete, being monitored by TLC, the N-1 synthon was added. Whereas ammonium nitrate **4a**, perchlorate **4b**, hydroxide **4c**, formate **4d**, chloride **4e**, and sulfate **4f** were ineffective (entries 1–6), the use of acetate **4g** and hydrogen carbonate **4h** gave, as expected, the desired isoquinoline **6a** in moderate yields (42–53%, entries 7 and 8).[11] More promising results were obtained with primary amines having a readily cleavable alkyl group such as 2,4,6-trimethoxybenzylamine hydrochloride **4i** and *tert*-butylamine **4j**,[7] leading to high yields of **6a**



Scheme 1 Construction of 3-(aminomethyl)isoquinolines by copper-catalysed four-component coupling–cyclisation.

Table 1 Optimisation of the N-1 synthon **4**[a]



Entry	N-1 synthon	Yield (%)[b]
1	NH_4NO_3 (**4a**)	Decomp.
2	NH_4ClO_4 (**4b**)	Decomp.
3	28% NH_4OH (**4c**)	Trace
4	$NH_4(HCO_2)$ (**4d**)	Trace
5	NH_4Cl (**4e**)	Trace
6	$(NH_4)_2SO_4$ (**4f**)	Trace
7	NH_4OAc (**4g**)	42
8	NH_4HCO_3 (**4h**)	53
9	2,4,6-$(MeO)_3C_6H_2CH_2NH_2 \cdot HCl$ (**4i**)	82
10	*t*-$BuNH_2$ (**4j**)	83

[a] After a mixture of 2-ethynylbenzaldehyde **1a**, paraformaldehyde **2** (2 equiv.), amine **3a** (2 equiv.) and CuI (10 mol%) in DMF was stirred at room temperature for 1 h, and N-1 synthon **4** (6 equiv.) was added. The resulting mixture was stirred for 5 h at room temperature and for an additional 45 min at 140 °C. [b] Isolated yield.

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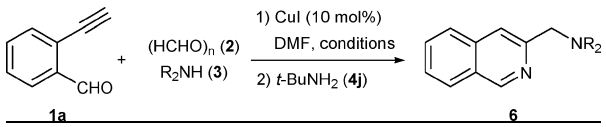
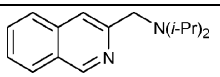
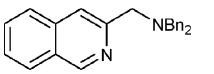
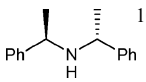
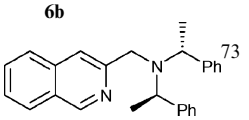
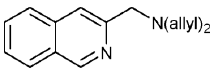
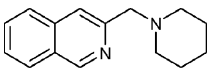
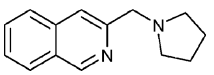
† Electronic supplementary information (ESI) available: Experimental details and NMR spectra. See DOI: 10.1039/b718201e

Table 2 Synthesis of 3-(aminomethyl)isoquinolines[a]



1a 6

Entry	Amine	Conditions[b]	Product	Yield (%)[d]
1	*i*-Pr$_2$NH (**3a**)	rt, 1 h	 (**6a**)	83
2	Bn$_2$NH (**3b**)	100 °C, 1 h	 (**6b**)	0
3	 (**3c**)	100 °C, 1 h	 (**6c**)	73
4	(allyl)$_2$NH (**3d**)	rt, 1 h[c]	 (**6d**)	60
5	 (**3e**)	rt, 1 h[c]	 (**6e**)	88
6	 (**3f**)	rt, 1 h[c]	 (**6f**)	79

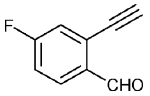
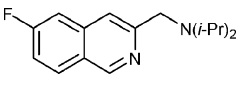
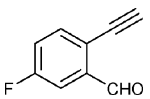
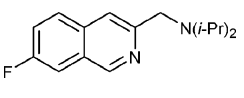
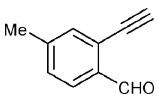
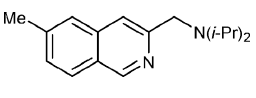
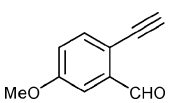
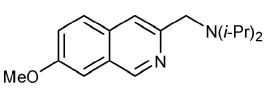
[a] After the three-component reaction of **1a**, **2** (2 equiv.), and **3** (2 equiv.) in the presence of CuI (10 mol%) in DMF was completed on TLC, *t*-BuNH$_2$ (**4j**, 6 equiv.) was added and the reaction mixture was stirred for 5 h at room temperature and for an additional 45 min at 140 °C. [b] Conditions for the three-component coupling. [c] Before **1a** was added, a mixture of **2**, **3** and CuI in DMF was stirred for 30 min at room temperature. [d] Isolated yield.

(entries 9 and 10).[12] Taking the atom economy of the reaction into consideration, we regarded **4j** as the most potent N-1 synthon.

Next, various secondary amines were employed to determine the scope of this reaction (Table 2). Although dibenzylamine **3b** showed lower reactivity toward Mannich-type coupling with **1a** and **2**, leading to recovery of the unchanged starting material (entry 2),[13] the reaction with more bulky bis(1-phenylethyl)amine **3c** led to successful conversion into the corresponding isoquinoline **6c** (73%, entry 3). Unfortunately, the initial Mannich type reaction with highly nucleophilic diallylamine, piperidine, or pyrrolidine was unsuccessful, producing a complex mixture, presumably due to the simultaneous presence of two aldehydes (2-ethynylbenzaldehyde **1a** and paraformaldehyde **2**) and a reactive amine. Extensive optimisation of the reaction conditions brought about addition of 2-ethynylaldehyde **1a** after the formation of iminium ions between secondary amines **3d–f** and paraformaldehyde **2**. As a result, the corresponding 3-(aminomethyl)isoquinolines **6d–f** were obtained in moderate to high yields (entries 4–6).

The copper-catalysed domino four-component syntheses of 3-(aminomethyl)isoquinolines with some substituted 2-ethynylbenzaldehydes were next investigated (Table 3). The use of 2-ethynyl-4-fluorobenzaldehyde **1b** in the presence of CuI (10 mol%) gave the desired 3-(aminomethyl)-6-fluoroisoquinoline derivative **7** in high yield (83%, entry 1). Benzaldehyde **1c**, which has a fluorine atom at the *meta*-position to the formyl group, afforded the corresponding isoquinoline **8** (79%, entry 2). Also, in the cases of 2-ethynylbenzaldehydes containing an electron-donating group such as a methyl or a methoxy group at the *para*- or *meta*-position to the formyl group (**1d** and **1e**, respectively), the copper-catalysed four-component isoquinoline formation proceeded smoothly (87 and 84% yield, respectively, entries 3 and 4). Thus, this isoquinoline formation was proven to be widely applicable to 2-ethynylbenzaldehydes having an electron-withdrawing and -donating group.

Table 3 Reactions with substituted 2-ethynylbenzaldehydes[a]

Entry	Substrate	Product	Yield (%)[b]
1	 (**1b**)	 (**7**)	83
2	 (**1c**)	 (**8**)	79
3	 (**1d**)	 (**9**)	87
4	 (**1e**)	 (**10**)	84

[a] After the three-component reaction of **1**, **2** (2 equiv.), and **3a** (2 equiv.) in the presence of CuI (10 mol%) in DMF was completed on TLC, *t*-BuNH$_2$ (**4j**, 6 equiv.) was added and the reaction mixture was stirred for 5 h at room temperature and for an additional 45 min at 140 °C. [b] Isolated yield.

In conclusion, we have developed a novel copper-catalysed domino four-component coupling–cyclisation reaction for the synthesis of 3-(aminomethyl)isoquinolines, which form one carbon–carbon and three carbon–nitrogen bonds. This methodology could be applied to the construction of a highly potent isoquinoline library in terms of diversity and biological activity.

Notes and references

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4 (*a*) M. A. H. de Zwart, H. van der Goot and H. Timmerman, *J. Med. Chem.*, 1989, **32**, 487–493; (*b*) J. E. van Muijlwijk-Koezen, H. Timmerman, R. Link, H. van der Goot and A. P. IJzerman, *J. Med. Chem.*, 1998, **41**, 3987–3993; (*c*) J. E. van Muijlwijk-Koezen, H. Timmerman, R. Link, H. van der Goot and A. P. IJzerman, *J. Med. Chem.*, 1998, **41**, 3994–4000.

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10 Actually, one-portion addition of all the four components using **4j** gave a complex mixture of unidentified products without producing **6** (compare with Table 1, entry 10).

11 For isoquinoline formation with such ammonium salts as formate, carbonate, and ammonia, see ref. 8*c*.

12 In the reaction using **4i**, a hydrogen atom at the 4-position of **6a** would come from H_2O generated in imine formation.

13 At the present stage of our understanding, the reason for this unsatisfactory result is unclear.