A domino synthesis of benzoquinolinamide in the presence of iodine†

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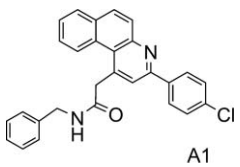
The domino synthesis of benzo[*f*]quinolinyl and benzo[*h*]quinolinyl acetamides from diketene, amines, aromatic aldehydes and naphthalenamine was developed, and the catalyst iodine was found to be crucial to the reaction. The structure was deduced from the mass spectrum, ^{1}H NMR, ^{13}C NMR spectrum and 2D NMR performed on two representative products.

Compared to traditional stepwise formation of individual bonds towards the construction of the target molecule, multi-component domino reactions allowing several bonds to be combined in a single sequence without isolation of intermediates give rise to complex structures accompanied by reducing the number of synthetic steps, energy consumption, and waste production. Accordingly, multi-component domino reactions, which lead to interesting heterocyclic scaffolds, have become a powerful tool for both chemists and biologists, since the main limitation of screening technology for drug discovery continues to lie in the capacity of the chemists to furnish biologists with a great diversity and number of products.[1]

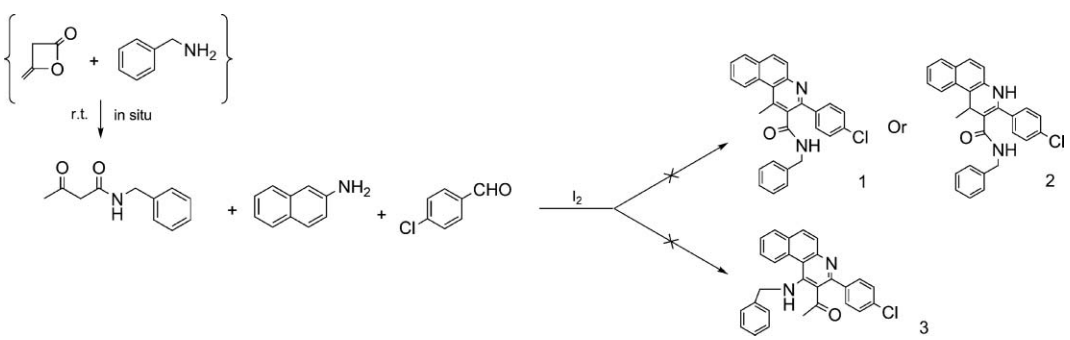
Many domino reaction products have drug-like structures, among which benzoquinoline and its derivatives exhibit interesting biological activities, including antibacterial, antimicrobial and antimalarial activities,[2] and inhibitory activity of recombinant human type 1 and 2 steriod 5a-reductase in vitro.[3] Recently, a series of benzo[*f*]quinoline derivatives has been synthesized by Wang and co-workers through three-component reaction of aromatic aldehyde, ketone and naphthalene-2-amine catalyzed by iodine.[4] On the other hand, diketene, readily ring-opened to react with amine in situ at room temperature, has been explored as a versatile synthetic building block for the construction of N-heterocyclic compounds.[5] Therefore, diketene was expected to introduce a new amide bond into benzoquinoline. The four components 4-chlorobenzaldehyde, naphthalene-2-amine, diketene and benzyl amine were treated as reported in the presence of iodine (Scheme 1). However, after isolation and analysis, *N*-benzyl-2-(3-(4-chlorophenyl)benzo[*f*]quinolin-1-yl)acetamide **A1** (Fig. 1) was obtained unexpectedly, which implied that the CH_3 was activated instead of CH_2 in the intermediate *N*-benzyl-3-oxobutanamide to construct the ring of pyridine. The ring-opening–recyclization process, occurring successively at the diketene ring in a very convenient manner, is of value to us not only because we are interested in the design of the iodine catalyzed new multicomponent reaction[6] but also because this new structure was normally difficult to prepare. Herein, we would like to present our preliminary results of this unprecedented approach to benzoquinolinamide.



A1

Fig. 1

The initial attempted reaction outlined in Scheme 1 was carried out in refluxing THF with the aim of fabricating the structure **1** or **2** in the same pathway as reported with 20 mol% of iodine. About 5 min later, the reaction mixture was solidified and 0.4 g of yellow solid was obtained after simple workup. The mass spectrum of the product displayed a molecular ion peak (positive) at the *m*/*z* value of 437, instead of 439, which confirmed that the aromatized pyridine-ring was formed just like structure **1**. However, the ^{1}H NMR spectrum confused us, as the anticipated signal arising from the CH_3 in structure **1** disappeared, and therefore, the alternative structure **3** containing a methyl was also rejected. After a detailed screening of the literature, we found that, in the structure of β-keto esters, the CH_3 could be activated by iodine rather than CH_2 to construct the benzo[*f*]quinoline,[4a] and accordingly, the



Scheme 1 Four-component reaction in the presence of iodine.

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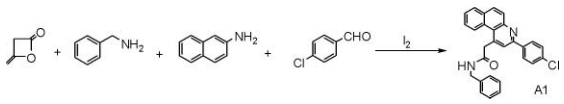
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and the copies of NMR for all the products. See DOI: 10.1039/c0ob00364f

Table 1 Conditional optimization of the four-component domino synthesis of *N*-benzyl-4-(4-chlorophenyl)-1,3-dihydrobenzo[*f*]furo[3,4-*c*]quinolin-3-amine in the presence of iodine[a]



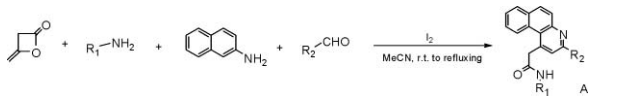
Entry	Iodine (mol%)	Solvent	T/°C [b]	t/min [c]	Yield (%) [d]
1	20	THF	65	8	46
2	0	THF	65	24 h	0
3	20	THF	25	10 h	29
4	20	EtOH	78	7	67
5	20	AcOEt	78	10	42
6	20	MeCN	78	5	72
7	25	MeCN	78	5	73
8	15	MeCN	78	8	36
9	10	MeCN	78	15	25
10	5	MeCN	78	30	21
11 [e]	20	MeCN	78	5	72

[a] Reaction conditions: after diketene (2 mmol) and amine (2 mmol) were stirred for 2 h in MeCN (5 ml), naphthalene-2-amine (2 mmol), aldehyde (2 mmol) and iodine (0.4 mmol) were added, and the temperature was then increased. [b] The temperature after all of the reactant was added. [c] The reaction time in refluxing MeCN. [d] Isolated yield. [e] The reaction was conducted under the protection of N_2.

structure **A1** was proposed, for the intermediate *N*-benzyl-3-oxobutanamide, ring-opened from diketene in situ, is structurally similar with β-keto esters. Fortunately, the structure **A1** was fully supported by the analysis of the NMR with the appearance of two sharp singlet signals in the ^{1}H NMR spectrum at δ = 4.3, 8.24 ppm; in the ^{13}C NMR spectrum at δ = 42.93, 124.69 ppm, arising from the CH_2 between the C═O and the pyridinyl ring, and the CH in the pyridinyl ring respectively. It was the CH_3, in the intermediate *N*-benzyl-3-oxobutanamide, that participated in the construction of the final structure unexpectedly, whereas the active methylene, which was supposed to be activated to attack the Schiff base intermediate according to the literature,[4,5] failed to build up the pyridine ring.

The surprising domino synthesis of the final structure and the considerable yield up to 46% prompted us to further investigate the reaction. Thereby, the optimization of the conditions was initially undertaken. As indicated in Table 1, the solvent, the temperature and the amount of iodine were evaluated, and the yield could be increased up to 72% in refluxing MeCN in the presence of 20 mol% of iodine.‡ The catalytic amount of iodine was found to be crucial, because no product was yielded without iodine (Table 1, Entry 2), and the aromatized structure **A1** was also produced when the reaction was performed under dry N_2 (Table 1, Entry 11). With the optimal conditions in hand, the amines and aldehydes were subsequently screened. The results collected in Table 2 verified the versatility of this strategy to prepare benzo[*f*]quinolinyl acetamide

Table 2 Iodine mediated four-component domino reaction to synthesize *N*,4-disubstituted-1,3-dihydrobenzo[*f*]furo[3,4-*c*]quinolin-3-amines[a]



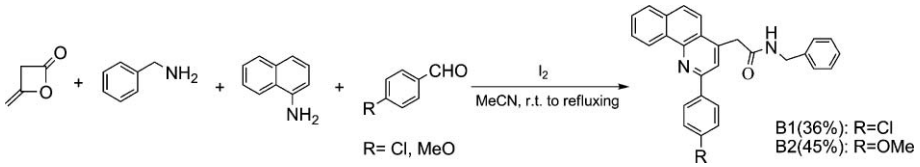
Entry	R_1	R_2	t/min [b]	Product	Yield (%) [c]
1	$C_6H_5CH_2$	4-ClC_6H_4	5	**A1**	72
2	$C_6H_5CH_2$	C_6H_5	10	**A2**	67
3	$C_6H_5CH_2$	4-MeOC_6H_4	5	**A3**	61
4	$C_6H_5CH_2$	4-$NO_2C_6H_4$	3	**A4**	50
5	$C_6H_5CH_2$	2-Cl C_6H_4	24 h	**A5**	0
6	$C_6H_5CH_2$	furyl	30	**A6**	52
7	4-Me(C_6H_4)	4-ClC_6H_4	2	**A7**	67
8	$CH_3(CH_2)_3$	4-ClC_6H_4	30	**A8**	64
9	2-naphthyl	4-ClC_6H_4	15	**A9**	66

[a] Reaction conditions: after diketene (2 mmol) and amine (2 mmol) were stirred for 2 h in MeCN (5 ml), naphthalene-2-amine (2 mmol), aldehyde (2 mmol) and iodine (0.4 mmol) were added, the temperature was then increased. [b] The reaction time in refluxing MeCN. [c] Isolated yield.

and derivatives. Most aromatic aldehydes were smoothly converted to the corresponding products including furan-2-carbaldehyde in moderate yield, while 2-chlorobenzaldehyde failed because of its steric properties. Meanwhile, selected amines including *p*-toluidine, butan-1-amine, and naphthalene-2-amine delivered satisfactory yields of the anticipated products.

Having established the scope and limitations we were able to perform a further comprehensive study by replacing naphthalene-2-amine with naphthalene-1-amine. As illustrated in Scheme 2, the transformation proceeded successfully when 4-chlorobenzylaldehye and 4-methoxybenzaldehyde were employed under standard conditions, whereas applying the same procedure to other aliphatic or aromatic amines resulted in a complex crude mixture from which no expected molecule was detected. All of the products were fully characterized by elemental analysis, mass spectrum and ^{1}H NMR, ^{13}C NMR spectrum, and the structures were further confirmed by ^{13}C DEPT90, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and HMBC, NOESY performed for two representative products *N*-benzyl-2-(3-(4-methoxyphenyl)benzo[*f*]quinolin-1-yl)acetamide **A3** and *N*-benzyl-2-(2-(4-methoxyphenyl)benzo[*h*]quinolin-4-yl)acetamide **B2**.[7]

Notably, the whole domino procedure was completed in no more than 30 min after the iodine was added. To our knowledge, this interesting structure benzoquinolinamide has not previously been reported, and the significant results, including the results from the experiments proceeding under the protection of N_2 as well as in the absence of iodine (Table 1, Entries 11 and 2), suggested that iodine played the most important role in promoting the 4-component domino reaction to this structure. However, the mechanism is



Scheme 2 The four-component domino reaction starting from naphthalene-1-amine.

uncertain, since the aromatization of the pyridine-ring occurred in the presence of catalytic iodine (20mol%) without oxygen. In comparison, Wang and co-workers observed that oxygen in air contributed to the aromatization of the pyridine-ring.

In conclusion, we have developed an interesting domino reaction of diketene, amines, aromatic aldehydes and naphthalenamine leading to benzo[*f*]quinolinyl and benzo[*h*]quinolinyl acetamides in the presence of iodine. The mild conditions, the short reaction time, the operational simplicity and the generality of the reaction should render this new domino reaction useful for introducing great molecular diversity. Further studies on the potential uses of the reaction in synthetic and medicinal chemistry are now in progress.

Acknowledgements

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Notes and references

‡ Representative procedure for the preparation of compound *N*-benzyl-2-(3-(4-chlorophenyl)benzo[*f*]quinolin-1-yl)acetamide **A1**. After a solution of benzyl amine (2 mmol) and diketene (2 mmol) was stirred in 5 ml of MeCN at room temperature for 2 h, naphthalene-2-amine (2 mmol) and 4-chlorobenzaldehyde (2 mmol) were added, the temperature was increased up to 82 °C, and then iodine (0.4 mmol) was added to the refluxing mixture. 3 min later, yellow precipitates were observed, and the reaction mixture was solidified in 5 min. The reaction was cooled to room temperature, and 2 ml of MeCN was added, the precipitates were isolated by filtration and washing with a solution of sodium thiosulfate followed by water and EtOH. The yellow product *N*-benzyl-2-(3-(4-chlorophenyl)benzo[*f*]quinolin-1-yl)acetamide **A1** was obtained after drying in 72% yield (0.63 g), and the purity of the corresponding product was high: up to 98% based on HPLC analysis. Mp 248–250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.35–4.36 (d, CH_2, J = 6.00 Hz, 2H), 4.60 (s, CH_2, 2H), 7.24–7.30 (m, aromatic, 5H), 7.62–7.74 (m, aromatic, 4H), 7.99–8.01 (d, aromatic, J = 4.00 Hz, 1H), 8.09–8.14 (m, aromatic, 2H), 8.24 (s, CH, 1H), 8.32–8.34 (m, aromatic, 2H), 8.69–8.71 (d, aromatic, J = 5.60 Hz, 1H), 8.82 (s, NH, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 42.93, 44.92, 124.69, 125.43, 126.02, 126.35, 126.74, 127.31, 127.5, 127.79,128.03, 128.13, 128.74, 129.18, 129.29, 129.61, 129.90, 129.93, 130.15, 132.81, 133.79, 134.76, 136.02, 139.75, 146.78, 147.60, 151.86, 169.07; MS (ESI$^+$) m/z 437(M + H); Anal. Calcd for $C_{28}H_{21}ClN_2O$: C, 76.97; H, 4.84; N, 6.41. Found: C, 76.91; H, 4.87; N, 6.50%.

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7 All of the products were new, the copies of 1D NMR for all of the compounds and the copies of 2D NMR for **A3** and **B2** see the supplementary material†.