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A Domino Process for the Sustainable Synthesis of Quinazolin-4(3*H*)-ones with Direct Chemo- and Regioselective Bromination

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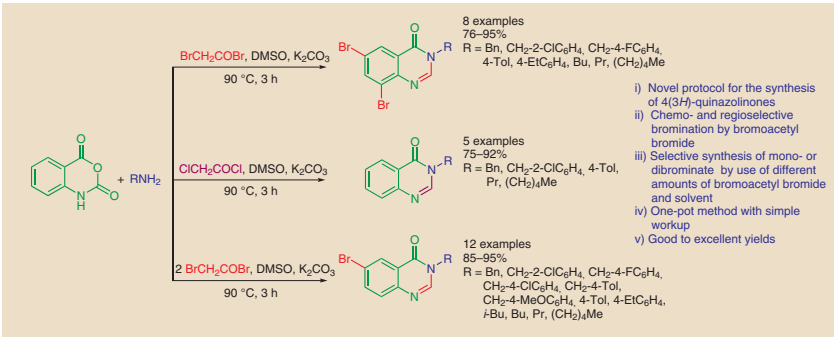

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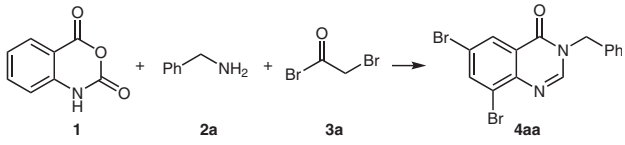
Abstract An efficient approach is reported for the direct and sustainable construction of quinazolin-4(3*H*)-ones through a three-component reaction of isatoic anhydride, primary amines, and bromoacetyl bromide or chloroacetyl chloride in the presence of K_2CO_3 in DMSO. With bromoacetyl bromide, mono- or dibrominated quinazolinone scaffolds were obtainable in a chemo- and regioselective manner.

Key words multicomponent reactions, quinazolinones, bromoacetyl bromide, regioselectivity, bromoquinazolines

Quinazolin-4(3*H*)-ones (QZs), as a significant series of benzo-fused N-containing heterocyclic compounds, are of interest because of their wide range of useful pharmacological and therapeutic activities, including anticancer,[1] anticonvulsant,[2] antioxidant,[3] antiinflammatory,[4] antitubercular,[5] antiulcer,[6] antiviral,[7] anti-HIV,[8] and antibiotic activities.[9] Febrifugine[10] and isofebrifugine[11] are two bioactive natural products that contain a quinazolinone moiety and possess antimalarial activity. Due to this wide range of applications, numerous synthetic routes have been developed for the preparation of these heterocycles.[12]

As part of our continuing effort to develop efficient methods for the preparation of biologically active organic compounds, we recently reported an oxidative process for the synthesis of 2,3-dihydroquinazoline-4-ones.[13] Here, we present a new route for the synthesis of QZs through a DMSO-based oxidative reaction. To achieve this goal, we studied the reaction between isatoic anhydride, primary amines, and bromoacetyl bromide or chloroacetyl chloride under various reaction conditions. These substrates are selectively linked through C–N bond-formation and C–C bond-cleavage steps, along with direct chemo- and regioselective bromination in the case of bromoacetyl bromide.

Table 1 Optimization of the Reaction of Isatoic Anhydride, Benzylamine, and Bromoacetyl Bromide in an Equimolar Ratio[a]



1 2a 3a 4aa

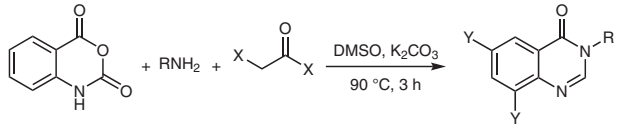
Entry	Solvent	Base (equiv)	Temp (°C)	Yield[b] (%)
1	DMSO	–	r.t.	NR[c]
2	DMSO	K_2CO_3 (0.5)	r.t.	NR
3	DMSO	K_2CO_3 (1.0)	r.t.	10
4	DMSO	K_2CO_3 (1.0)	50	11
5	DMSO	K_2CO_3 (1.0)	90	13
6	DMSO	K_2CO_3 (1.0)	50	70
7	DMSO	K_2CO_3 (1.0)	90	95
8	DMSO	K_2CO_3 (1.0)	100	94
9	DMSO	K_2CO_3 (1.0)	120	80
10	DMF	K_2CO_3 (1.0)	90	13
11	toluene	K_2CO_3 (1.0)	90	13
12	1,4-dioxane	K_2CO_3 (1.0)	90	NR
13	H_2O	K_2CO_3 (1.0)	90	NR
14	DMSO	Et_3N (1.0)	90	48
15	DMSO	*t*-BuOK (1.0)	90	33
16	DMSO	DBU (1.0)	90	51
17	DMSO	piperidine (1.0)	90	50

[a] Reaction conditions: (entries 1–5) **1** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), base, DMSO (3 mL), 3 h. (entries 6–17): **1** (1 mmol) and **2a** (1 mmol), solvent (3 mL), 1 h; then **3a** (1 mmol), base (1 mmol), stirring, 2 h.
[b] Isolated yield.
[c] NR = No reaction.

Initially, we chose the reaction between isatoic anhydride (**1**), benzylamine (**2a**), and bromoacetyl bromide (**3a**) as a model reaction, and we tested several reaction conditions (Table 1). To our delight, the doubly brominated QZ **4aa** was detected in 95% yield when **1** and **2a** were treated in DMSO at 90 °C for one hour, followed by subsequent addition of **3a** and K_2CO_3 and stirring the mixture under the same conditions for a further two hours (entry 7).

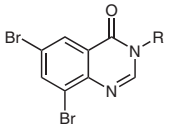
Having pinpointed the optimal conditions, we then investigated the scope of the reaction by using various primary amines **2** with bromoacetyl bromide (**3a**) or chloroacetyl chloride (**3b**) for this three-component reaction in the presence of K_2CO_3 in DMSO at 90 °C (Table 2). We found that when one equivalent of **3a** was used, the dibrominated products **4aa–ah** were obtained; whereas when one equivalent of **3b** was used, chlorination did not occur (**4ba–be**). All the QZs **4aa–be** were obtained in good to excellent yields.[14]

Table 2 Synthesis of QZs **4aa–ah** and **4ba–be** by the use of **3a** or **3b**[a]



1 **2** **3a**, X = Br; **3b**, X = Cl **4a**, Y = Br; **4b**, Y = H

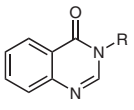
X = Br (**3a**); Y = Br



4a

4aa: R = Bn, 95%
4ab: R = CH_2-2-ClC_6H_4, 85%
4ac: R = CH_2-4-FC_6H_4, 78%
4ad: R = 4-Tol, 91%
4ae: R = 4-EtC_6H_4, 84%
4af: R = Bu, 78%
4ag: R = Pr, 80%
4ah: R = $(CH_2)_4Me$, 76%

X = Cl (**3b**); Y = H



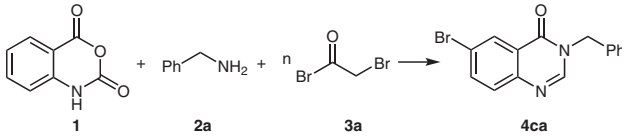
4b

4ba: R = Bn, 88%
4bb: R = CH_2-2-ClC_6H_4, 83%
4bc: R = Pr, 81%
4bd: R = $(CH_2)_4Me$, 75%
4be: R = 4-Tol, 92%

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), DMSO (3 mL), 90 °C, 1 h; then **3** (1 mmol), K_2CO_3 (1 mmol), stirring (90 °C), 2 h.
[b] Isolated yield.

Next, the three-component reaction was carried out with an excess of **3a** (for optimization of the reaction conditions, see Table 3). Surprisingly, we found that the reaction of **3a** (2 equiv) in the presence of K_2CO_3 in DMSO (1.5 mL) afforded the monobrominated QZ **4ca** in 94% yield (Table 3, entry 8).

Table 3 Optimization of the Reaction Between Isatoic Anhydride, Benzylamine, and Excess Bromoacetyl Bromide[a]



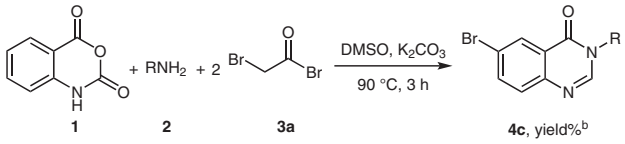
1 **2a** **3a** **4ca**

Entry	**3a** (equiv)	DMSO (mL)	Yield[b] (%)
1	2	3	NC[c]
2	2.5	3	31
3	3	3	48
4	3	2.5	53
5	3	2	65
6	3	1.5	87
7	2.5	1.5	89
8	2	1.5	94

[a] Reaction conditions: **1** (1 mmol), **2a** (1 mmol), DMSO, 90 °C, 1 h; then, **3a**, K_2CO_3 (1 mmol), stirring, 2 h.
[b] Isolated yield.
[c] NC = Nonclean reaction.

By use of **1**, **2**, and two equivalents of **3a**, the monobrominated QZs **4ca–cl** were obtained in high yields (Table 4). In addition, the reaction between **1**, benzylamine (**2a**), and **3b** (2 equiv) gave **4ba**.

Table 4 Synthesis of Monobrominated QZs **4ca–cl**[a,b]



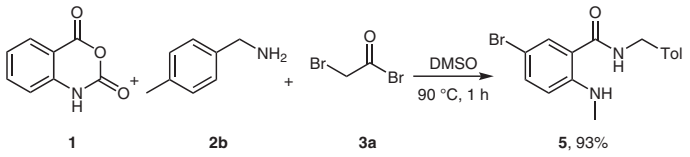
1 **2** **3a** **4c**, yield%[b]

4ca: R = Bn, 94%	**4cb**: R = CH_2-2-ClC_6H_4, 90%
4cc: R = CH_2-4-FC_6H_4, 85%	**4cd**: R = CH_2-4-Tol, 95%
4ce: R = CH_2-4-ClC_6H_4, 91%	**4cf**: R = 4-Tol, 89%
4cg: R = 4-EtC_6H_4, 85%	**4ch**: R = 4-$MeOC_6H_4$, 87%
4ci: R = *i*-Bu, 90%	**4cj**: R = Bu, 93%
4ck: R = Pr, 95%	**4cl**: R = $(CH_2)_4Me$, 90%

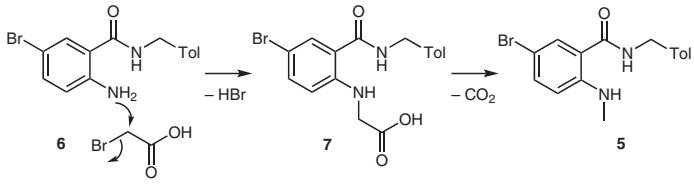
[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), DMSO (1.5 mL), 90 °C, 1 h; then **3a** (2 mmol), K_2CO_3 (1 mmol), stirring, 90 °C, 2 h.
[b] Isolated yields are reported.

The bromination occurred chemoselectively in the benzo ring of the QZ, and regioselectively at the C6 and C8 positions for dibromination and at the C6 position for monobromination.

In the monobrominated adducts **4c**, *para*-selective bromination was confirmed on the basis of chemical shifts and coupling patterns for the three hydrogen atoms on the phenylene ring in the ^1H NMR spectra of these compounds. For example, in the ^1H NMR spectrum of **4cc**, the most



Scheme 1 The reaction between **1**, **2b** and **3a** in the absence of K_2CO_3



Scheme 2 Proposed mechanism for the formation of **5** in the absence of K_2CO_3

deshielded hydrogen (H5, *ortho* to the carbonyl group) resonated at δ = 8.45 ppm as a doublet with $^4J_{meta}$ = 2.3 Hz. The hydrogen atom H7 was observed as a doublet of doublets at δ = 7.84 with $^3J_{ortho}$ = 8.7 Hz and $^4J_{meta}$ = 2.3 Hz. The hydrogen atom H8 appeared as a doublet at δ = 7.59 with $^3J_{ortho}$ = 8.7 Hz (Figure S1 in the Supporting Information).

We also examined the reaction of isatoic anhydride (**1**), 4-methylbenzylamine (**2b**), and one or two equivalents of bromoacetyl bromide (**3a**) in DMSO in the absence of K_2CO_3; this gave the N-methylated anthranilamide **5** exclusively (Scheme 1).

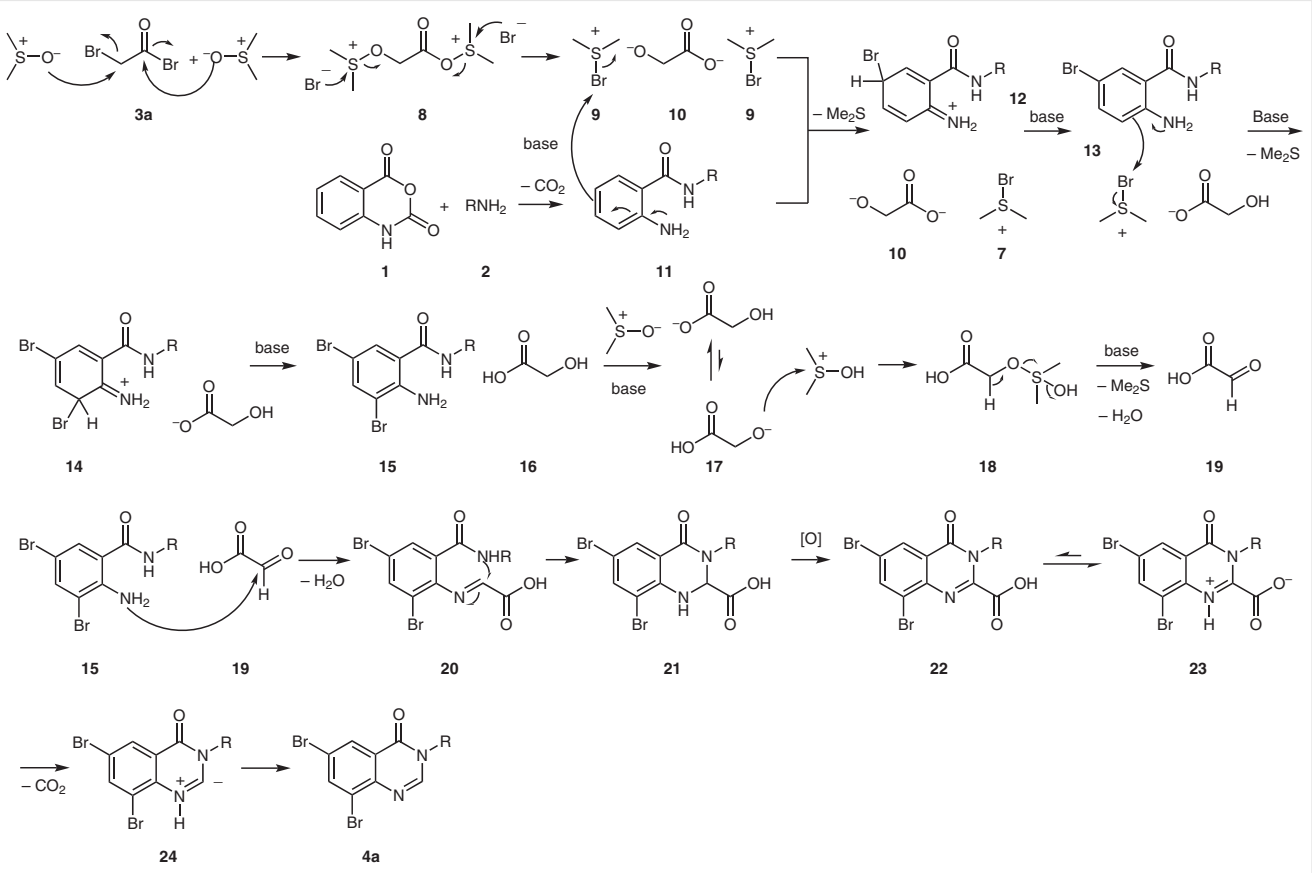
The formation of **5** can be explained by alkylation of the monobrominated QZ **6** by bromoacetic acid generated in situ to give the *N*-arylated glycine intermediate **7**, which undergoes decarboxylation under the reaction conditions to afford **5** (Scheme 2)

These transformations and the formation of the quinazolin-4(3*H*)-one scaffold probably involve a complex multistep sequence of events. On the basis of our results, a possible mechanism for the formation of the dibrominated QZ **4a** is shown in Scheme 3. It is reasonable to assume that the reaction of **3a** with two DMSO molecules forms intermediate **8**, which undergoes nucleophilic addition by the bromide anions to generate two molecules of the electrophilic bromodimethylsulfonium species **9** and the glycolic acid dianion **10**. Then, anthranilamide **11**, generated by nucleophilic addition of amine **2** to isatoic anhydride **1**, undergoes two electrophilic substitutions by the two BDMS molecules **9** to give the dibrominated anthranilamide **15** via intermediates **12**–**14**. Next, the glycolic acid **16** generated in situ might undergo a Kornblum-type oxidation[15] by DMSO under the reaction conditions to produce glyoxylic acid (**19**) via **17** and **18**. Glyoxylic acid (**19**) might be attacked by anthranilamide **15** to give oxotetrahydroquinazoline-2-carboxylic acid **21**, which, in turn, might be oxidized to the oxodihydroquinazolin-2-carboxylic acid **22**. Carboxylic acid **22** might undergo thermal decarboxylation[16] to afford QZ **4a** via **23** and **24**. In a control experiment, dibrominated anthranilamide **15** (R = Bn) was prepared according to the reported procedure[17] and treated with glyoxylic acid (**19**) under the reaction conditions to give QZ **4a** in 96% yield.

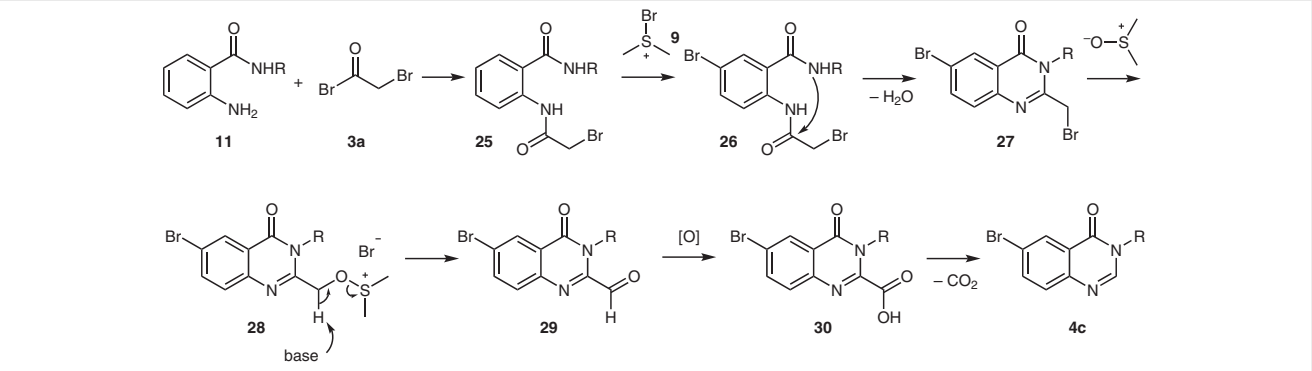
A reasonable mechanism for the formation of monobrominated QZs **4c** is provided in Scheme 4. First, in the presence of an excess of the acylation reagent **3a** in a smaller quantity of DMSO, the anthranilamide **11** might be acylated to yield amide intermediate **25**. Due to both acylation and steric factors, amide **25** has a lower reactivity toward aromatic electrophilic bromination than does the corresponding amine **11** and might therefore undergo monobromination by bromodimethylsulfonium **9** to give **26**. Intramolecular cyclization and dehydration might then give 2-bromomethylquinazolin-4(3*H*)-one **27**; this might undergo Kornblum oxidation in the presence of K_2CO_3 to give 4(3*H*)-oxoquinazolin-2-carboxaldehyde **29** via **28**. Oxidation converts **29** into 4(3*H*)-oxoquinazolin-2-carboxylic acid **30**, which undergoes thermal decarboxylation to afford QZ **4c**.

In the case of **3b**, the formation of a QZ with no chlorination might result from the lower activity of the chloride anion in comparison with that of the bromide anion for the formation of the corresponding halodimethylsulfonium species.

In conclusion, we have devised an efficient one-pot synthesis of QZs with direct chemo- and regioselective bromination. This can be regarded as a new and direct approach for the preparation of synthetically and pharmaceutically relevant QZ scaffolds. Advantages of the method include its simple starting materials, short reaction times, simple procedures and workup, and good to excellent yields of products, along with chemo- and regioselectivity and a controllable degree of bromination. We hope that this protocol might be of value to others seeking novel synthetic scaffolds with unique properties for pharmaceutical chemistry programs.



Scheme 3 Proposed mechanism for the formation of dibrominated QZs **4a**



Scheme 4 Proposed mechanism for the formation of monobrominated QZs **4c**

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610226.

References and Notes

(1) (a) Cao, S.-L.; Feng, Y.-P.; Jiang, Y.-Y.; Liu, S.-Y.; Ding, G.-Y.; Li, R.-T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1915. (b) Zahedifard, M.; Faraj, F. L.; Paydar, M.; Looi, C. Y.; Hajrezaei, M.; Hasanpourghadi, M.; Kamalidehghan, B.; Majid, N. A.; Ali, H. M.; Abdulla, M. A. *Sci. Rep.* **2015**, *5*, 11544.

(2) Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. *J. Med. Chem.* **1990**, *33*, 161.

(3) Kumar, A.; Sharma, P.; Kumari, P.; Kalal, B. L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4353.
(4) Ozaki, K.-i.; Yamada, Y.; Oine, T.; Ishizuka, T.; Iwasawa, Y. *J. Med. Chem.* **1985**, *28*, 568.
(5) Kuneš, J.; Bažant, J.; Pour, M.; Waisser, K.; Šlosárek, M.; Janota, J. *Farmaco* **2000**, *55*, 725.
(6) Tereshima, K.; Shimamura, H.; Kawase, A.; Tanaka, Y.; Tanimura, T.; Kamisaki, T.; Ishizuka, Y.; Sato, M. *Chem. Pharm. Bull.* **1995**, *43*, 2021.
(7) Wang, Z.; Wang, M.; Yao, X.; Li, Y.; Tan, J.; Wang, L.; Qiao, W.; Geng, Y.; Liu, Y.; Wang, Q. *Eur. J. Med. Chem.* **2012**, *53*, 275.
(8) Pati, B.; Banerjee, S. *J. Adv. Pharm. Educ. Res.* **2013**, *3*, 136.
(9) Bouley, R.; Kumarasiri, M.; Peng, Z.; Otero, L. H.; Song, W.; Suckow, M. A.; Schroeder, V. A.; Wolter, W. R.; Lastochkin, E.; Antunes, N. T.; Pi, H.; Vakulenko, S.; Hermoso, J. A.; Chang, M.; Mobashery, S. *J. Am. Chem. Soc.* **2015**, *137*, 1738.
(10) Kikuchi, H.; Yamamoto, K.; Horoiwa, S.; Hirai, S.; Kasahara, R.; Hariguchi, N.; Matsumoto, M.; Oshima, Y. *J. Med. Chem.* **2006**, *49*, 4698.
(11) Chen, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 12546.
(12) (a) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686. (b) Adib, M.; Karimzadeh, M.; Mahdavi, M.; Sheikhi, E.; Mirzaei, P. *Synlett* **2011**, 834. (c) Adib, M.; Sheikhi, E.; Bijanzadeh, H. R. *Synlett* **2012**, 85. (d) Wang, H.; Cao, X.; Xiao, F.; Liu, S.; Deng, G.-J. *Org. Lett.* **2013**, *15*, 4900. (e) He, L.; Li, H.; Neumann, H.; Beller, M.; Wu, X.-F. *Angew. Chem. Int. Ed.* **2014**, *53*, 1420. (f) Feng, Y.; Li, Y.; Cheng, G.; Wang, L.; Cui, X. *J. Org. Chem.* **2015**, *80*, 7099. (g) Li, Z.; Dong, J.; Chen, X.; Li, Q.; Zhou, Y.; Yin, S.-F. *J. Org. Chem.* **2015**, *80*, 9392. (h) Srishylam, V.; Devanna, N.; Rao, M. V. B.; Mulakayala, N. *Tetrahedron Lett.* **2017**, *58*, 2889.
(13) Rezaei, N.; Sheikhi, E.; Ranjbar, P. R. *Synlett* **2018**, *29*, 912.

(14) **Dibrominated 4(3*H*)-Quinazolinone 4aa–ah; General Procedure**

A mixture of isatoic anhydride (**1**; 1 mmol) and the appropriate primary amine **2** (1 mmol) in DMSO (3 mL) was stirred at 90 °C for 1 h. $BrCH_2COBr$ (**3a**; 1 mmol) and K_2CO_3 (1 mmol) were added, and the mixture was stirred at 90 °C for a further 2 h. When the reaction was complete (TLC), the mixture was cooled to r.t. and the reaction was quenched with H_2O (3 mL). The mixture was then stirred for 10 min at r.t., and the resulting precipitate was collected by filtration, washed with H_2O, dried, and crystallized from EtOH.

3-Benzyl-6,8-dibromoquinazolin-4(3*H*)-one (4aa)

White solid; yield: 0.374 g (95%); mp 173–175 °C (Lit.[1] 176.5–178.5 °C). IR (KBr): 1679 (C=O), 1596 (C=N), 1540, 1492, 1443, 1360, 1306, 1254, 1170, 1142, 1076, 1029, 996, 958, 875, 811, 723, 693, 670, 627 cm^{-1}. ^1H NMR (300.1 MHz, $CDCl_3$): δ = 5.21 (s, 2 H, CH_2), 7.37–7.41 (m, 5 H, 5CH), 8.16 (d, *J* = 2.1 Hz, 1 H, CH), 8.24 (s, 1 H, NCHN), 8.44 (d, *J* = 2.1, 1 H, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 50.1 (CH_2), 120.8, 123.4 and 124.4 (3 C), 128.2 (2CH), 128.7 (CH), 129.2 (2CH and CH), 134.9 (C), 140.4 (CH), 144.7 (C), 147.3 (NCHN), 159.4 (C=O). EI-MS, *m/z* (%): 396 [M^+, $^{81}Br_2$] (17), 394 [M^+, $^{81}Br^{79}Br$] (35), 392 [M^+, $^{79}Br_2$] (19), 315 (4), 288 (4), 234 (4), 116 (1), 104 (1), 91 (100), 74 (3), 65 (14), 51 (3). Anal. Calcd for $C_{15}H_{10}Br_2N_2O$ (394.06): C, 45.72; H, 2.56; N, 7.11. Found: C, 45.66; H, 2.43; N, 7.02.

(15) (a) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113. (b) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562.
(16) Hollóczki, O.; Nyulászi, L. *J. Org. Chem.* **2008**, *73*, 4794.
(17) Liangzhong, X.; Shuai, T.; Wang, M. CN 105153113B, **2016**.