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Metal-Free Mild Synthesis of Novel 1′*H*-Spiro[Cycloalkyl-1,2′-quinazolin]-4′(3′*H*)-ones by an Organocatalytic Cascade Reaction

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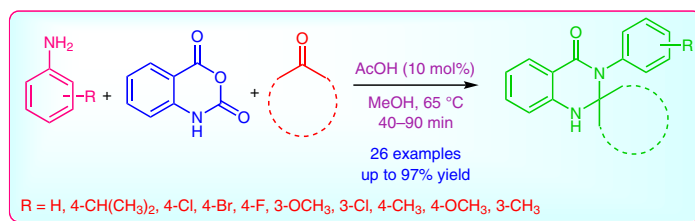
R = H, 4-CH(CH₃)₂, 4-Cl, 4-Br, 4-F, 3-OCH₃, 3-Cl, 4-CH₃, 4-OCH₃, 3-CH₃

Abstract A concise organocatalytic method for the facile synthesis of some novel 1′*H*-spiro[cycloalkyl-1,2′-quinazolin]-4′(3′*H*)-ones via a one-pot, three-component condensation of isatoic anhydride, aryl or aliphatic amines and a cyclic ketone is described.

Key words spiro compounds, quinazolinones, isatoic anhydride, amines, cycloalkanones, multicomponent reactions

The exploration of synthetic efficiency while minimizing needless synthetic steps is key to the synthesis of complex organic skeletons.[1] One-step synthetic strategies are increasingly used to access drug-like molecules.[2] Specifically, heterocyclic frameworks bearing spiro centers possess structural rigidity resulting from conformational restriction, and they have consequently received attention due to their enhanced activities against a number of pharmacological targets.[3]

Spiroquinazolinones and their derivatives constitute a privileged class of fused heterocycles, as they possess notable biological properties, especially antimicrobial activities.[4] Such scaffolds have been explored as core structures and have been extensively studied in many bioactive natural and synthetic molecules.[5] Quinazolinones present numerous biological actions, such as antitumor,[6,7] antifibrillatory,[8] antidepressant,[9] analgesic,[10] diuretic,[11] antihistamine,[12] vasodilatory,[13] antihypertensive,[14] CNS-stimulant,[15] tranquilizing,[16] anxiolytic,[17] and plant-growth-regulating[18] activities. In addition, quinazolin-4(3*H*)-ones are useful synthetic precursors.[19–23] In continuation of our interest in the design and synthesis of heterocyclic candidates,[24] we describe an efficient and scalable cascade strategy for the synthesis of diversely functionalized 1′*H*-spiro[cycloalkyl-1,2′-quinazolin]-4′(3′*H*)-one derivatives through a one-pot

condensation of isatoic anhydride, an aryl or aliphatic amine, and a cyclic ketone in the presence of a catalytic amount of acetic acid.

We started our study by investigating the 4-toluenesulfonic acid (PTSA)-catalyzed three-component reaction of aniline (**1a**), isatoic anhydride (**2**), and cyclohexanone (**3**) as model substrates in ethanol at reflux temperature. We found that the desired product **4a** was obtained in 51% yield after heating at reflux for two hours. In attempts to increase the reaction efficiency, we studied sulfamic acid and acetic acid as catalysts (Table 1, entries 2–4). From these observations, it was clear that acetic acid (20 mol%) gave the best yield (91%) in the shortest reaction time (entry 4). Subsequently, we screened a range of polar solvents (ethanol, methanol, acetonitrile, and propan-2-ol) (entries 4–7) and we found that methanol was the most efficient solvent for

**Table 1** Optimization of Reaction Conditions for Synthesis of Spiro Product **4a**[a]

Entry	Catalyst (mol %)	Solvent	Time (min)	Yield[b] (%)
1	–	EtOH	180	trace
2	PTSA (20)	EtOH	120	51
3	NH₂SO₃H (20)	EtOH	120	57
4	AcOH (20)	EtOH	75	91
5	AcOH (20)	MeOH	60	94
6	AcOH (20)	MeCN	120	84
7	AcOH (20)	*i*-PrOH	120	79
8	AcOH (5)	MeOH	90	83
9	AcOH (10)	MeOH	60	93
10	AcOH (15)	MeOH	60	94

[a] Reaction conditions: isatoic anhydride (**2**; 3 mmol), aniline (**1a**; 3 mmol), cyclohexanone (**3**; 3 mmol), solvent (10 mL), catalyst, reflux.
[b] Isolated yield.

this condensation, affording the desired spiro product **4a** in 94% yield (entry 5). Screening the quantity of the catalyst showed that a yield of 93% was obtained by using 10 mol% of acetic acid (entry 9). We also attempted to reduce the reaction temperature from reflux to ambient temperature, but the reaction was sluggish and the yield decreased (not shown). Hence, the optimal conditions were determined to be refluxing methanol containing 10 mol% of acetic acid as the catalyst.

After the optimization studies, the synthesis of a variety of functionalized 1′*H*-spiro[cyclohexane-1,2′-quinazolin]-4′(3′*H*)-ones[25,26] was performed to explore the efficiency and versatility of this method (Scheme 1), and the results are presented in Table 2. Various aromatic amines bearing either electron-withdrawing or electron-donating substituents successfully afforded the corresponding products **4b–j** in good to excellent yields (Table 2, entries 2–10). In contrast, aliphatic amines **1k** and **1l** (Table 2, entries 11 and 12) provided only moderate yields, presumably due to their higher nucleophilicity compared with aryl amines. The products were characterized by means of ¹H and ¹³C NMR spectroscopy and by X-ray single-crystal analysis.
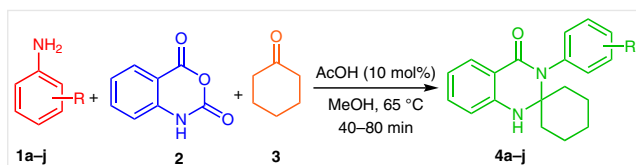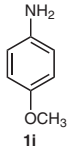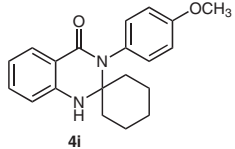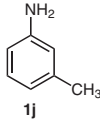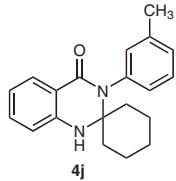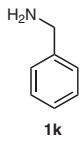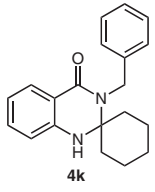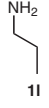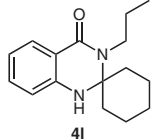

Scheme 1 Acetic acid-assisted three-component synthesis of 3′-aryl-1′*H*-spiro[cyclohexane-1,2′-quinazolin]-4′(3′*H*)-ones

In the ¹H NMR spectrum of compound **4b**, as a representative example, the aliphatic protons (–CH₂–) of the cyclohexane moiety appeared as multiplets at δ = 0.91, 1.25, 1.55, and 2.04 ppm; the secondary amine (–NH–) proton appeared as a singlet at δ = 7.01 ppm; and the aromatic protons were observed as multiplets at δ = 6.68–7.65 ppm. In the ¹³C NMR spectrum, the carbons in the cyclohexane ring appeared as resonances at δ = 21.1, 24.0 and 34.5 ppm, and the amide carbon (–CONX) exhibited as a peak at δ = 162.8 ppm. Furthermore, the structures of compounds **4a** (Figure 1) and **4e** (Figure 2) were confirmed by single-crystal X-ray analysis.[27]

To extend the scope of the reaction, we applied the optimized protocol to the synthesis of 1′*H*-spiro[cyclopentane-1,2′-quinazolin]-4′(3′*H*)-ones by reaction with cyclopentanone (**5**; Scheme 2). Aromatic amines **1a–j** bearing various functional groups at various positions reacted with isatoic anhydride (**2**) smoothly in the presence of cyclopentanone (**5**), and the corresponding targets (**6a–j**) were obtained. The results are summarized in Table 3.
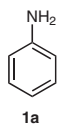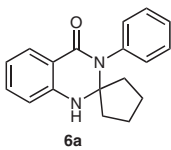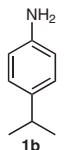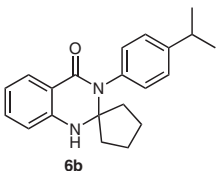
Table 2 Synthesis of 1′*H*-Spiro[cyclohexane-1,2′-quinazolin]-4′(3′*H*)-one Derivatives[a]
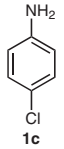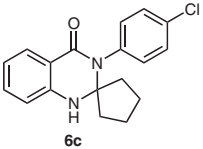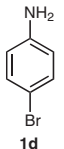
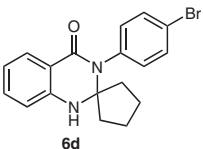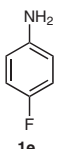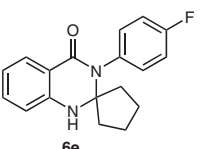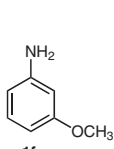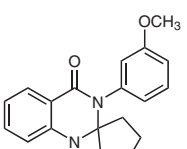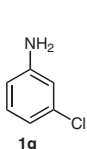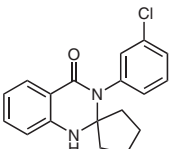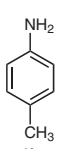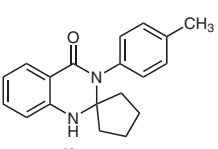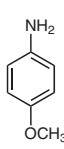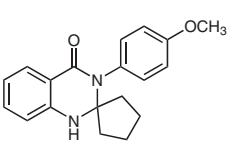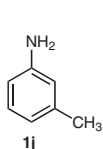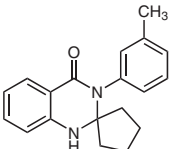| Entry	Amine	Product	Time (min)	Yield[b] (%)
1	1a	4a	60	93
2	1b	4b	75	91
3	1c	4c	40	96
4	1d	4d	45	95
5	1e	4e	40	96
6	1f	4f	80	89
7	1g	4g	45	93
8	1h	4h	75	90

Entry	Amine	Product	Time (min)	Yield[b] (%)		Entry	Amine	Product	Time (min)	Yield[b] (%)
9	1i	4i	80	88		3	1c	6c	45	97
10	1j	4j	80	86		4	1d	6d	45	94
11	1k	4k	90	84		5	1e	6e	45	95
12	1l	4l	90	81		6	1f	6f	85	90
						7	1g	6g	50	92
						8	1h	6h	80	89
						9	1i	6i	90	86
						10	1j	6j	90	85
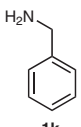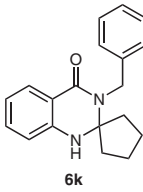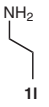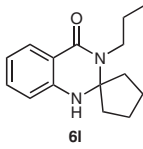
[a] Reaction conditions: isatoic anhydride (2; 3 mmol), amine 1 (3 mmol), cyclohexanone (3; 3 mmol), AcOH (10 mol%), MeOH (10 mL), reflux.
[b] Isolated yield.

Table 3 Synthesis of 1′H-Spiro[cyclopentane-1,2′-quinazolin]-4′(3′H)-one Derivatives[a]

Entry	Amine	Product	Time (min)	Yield[b] (%)
1	1a	6a	60	91
2	1b	6b	80	94

Entry	Amine	Product	Time (min)	Yield[b] (%)
11	**1k**	**6k**	95	86
12	**1l**	**6l**	110	81

[a] Reaction conditions: isatoic anhydride (**2**; 3 mmol), amine (**1**; 3 mmol), cyclopentanone (**5**; 3 mmol) AcOH (10 mol%), MeOH (10 mL), reflux.
[b] Isolated yields.

The ^{1}H NMR spectrum of compound **6b** showed multiplets at δ = 1.43, 1.71, and 1.89 ppm corresponding to the aliphatic protons of the cyclopentane group. The secondary amine (–NH–) proton appeared as a singlet at δ = 6.93 ppm, and the aromatic protons appeared as multiplets at δ = 6.69–7.67 ppm. In the ^{13}C NMR spectrum, the amide carbon (–CONX) was evident as a resonance at δ = 163.0 ppm.[29] Moreover, the structure of **6e** was confirmed by single-crystal X-ray analysis (Figure 3).
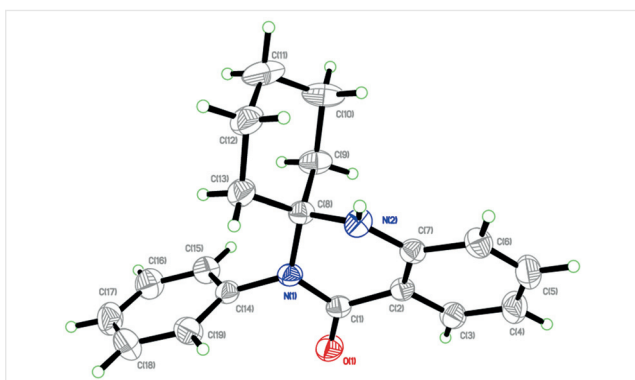
Figure 1 ORTEP of compound **4a** (CCDC 1543174)[28]
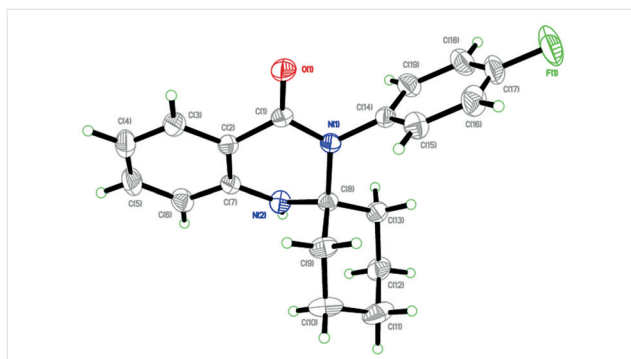
Figure 2 ORTEP of compound **4e** (CCDC 1543282)[28]
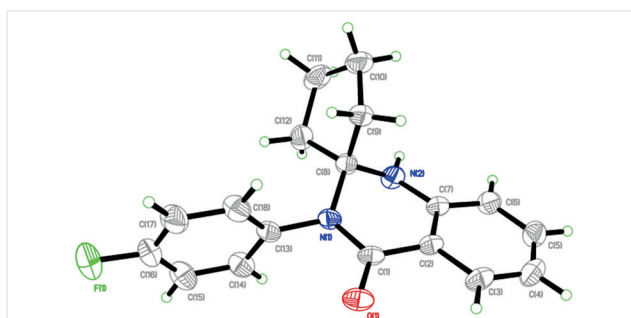
Figure 3 ORTEP of compound **6e** (CCDC 1543283)[28]

Finally, we examined the reaction with benzene-1,4-diamine (**7**) instead of an aromatic monoamine (Scheme 3), and this pseudo-five-component reaction led to the novel bis{1′*H*-spiro[cycloalkane-1,2′-quinazolin]-4′(3′*H*)-ones} **8** and **9** in good yields. Their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopic analyses.

In conclusion, we have disclosed an efficient and concise approach for the one-pot synthesis of various 1′*H*-spiro[cycloalkyl-1,2′-quinazolin]-4′(3′*H*)-one derivatives
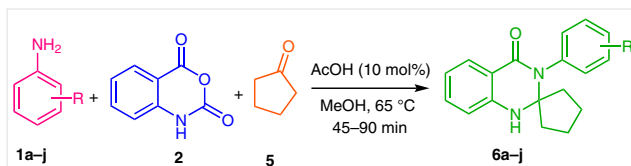
Scheme 2 Three-component synthesis of 3′-aryl-1′*H*-spiro[cyclopentane-1,2′-quinazolin]-4′(3′*H*)-ones
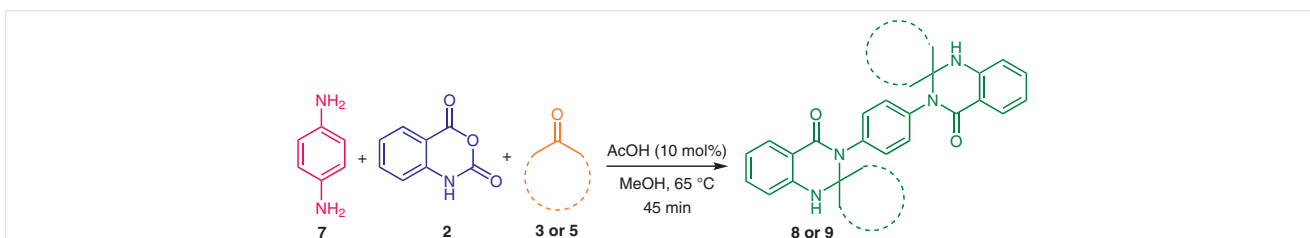
Scheme 3 Pseudo-five-component synthesis of bis[1′*H*-spiro[1,2′-quinazolin]-4′(3′*H*)-ones]

through a three-component reaction in the presence of a catalytic amount of acetic acid. The method tolerates an array of functional groups and has the advantages of mild reaction conditions, short reaction times, experimental simplicity, and excellent yields.

Acknowledgment

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590917.

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(25) **1′H-Spiro[cycloalkyl-1,2′-quinazolin]-4′(3′H)-ones 4a–l and 6a–l; General Procedure**
A 50 mL round-bottomed flask was charged with MeOH (5 mL), isatoic anhydride (**2**; 3 mmol), the appropriate amine **1** (3 mmol), and AcOH (10 mol%), and the mixture was stirred at r.t. for about 5 min. Cyclohexanone or cyclopentanone (3 mmol) in MeOH (5 mL) was added, and the resulting mixture was stirred at the reflux temperature until the reaction was complete [TLC; EtOAc–hexane (3:7); see Tables 2 and 3]. The mixture was allowed to cool to r.t., and the resulting solid was collected by filtration. The crude product was purified by crystallization from EtOH.

(26) **3′-(4-Isopropylphenyl)-1′H-spiro[cyclohexane-1,2′-quinazolin]-4′(3′H)-one (4b)**
Colorless crystals; yield: 914 mg (91%); mp 208–210 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.91 (d, J = 12.0 Hz, 1 H, CH$_2$), 1.23 (d, J = 6.8 Hz, 6 H, CH$_2$), 1.29 (d, J = 12.4 Hz, 2 H, CH$_2$), 1.55 (m, 5 H, CH$_2$), 2.01 (d, J = 12.0 Hz, 2 H, CH), 2.91 (m, 1 H, CH), 6.68 (s, 1 H, ArH), 6.70 (s, 1 H, NH), 7.03 (m, 3 H, ArH), 7.27 (d, J = 6.8 Hz, 3 H, ArH), 7.63 (t, J = 7.2 Hz, 1 H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.1, 23.7, 24.0, 32.9, 34.5, 72.9, 115.1, 115.6, 117.1, 126.4, 127.5, 130.0, 132.9, 135.7, 145.5, 147.3, 162.8. Anal. Calcd for C$_{22}$H$_{26}$N$_2$O (334.45): C 79.0, H 7.84, N 8.38; Found: C 79.44, H 8.15, N 8.76.

(27) Crystals of compounds **4a**, **4e**, and **6e** were mounted on a Gemini A Ultra Oxford Diffraction automatic diffractometer equipped with a CCD detector. Data were collected with graphite-monochromated MoKα radiation (λ = 0.71073 Å) at 295(2) K with an ω scan mode. Lorentz, polarization, and empirical absorption corrections using spherical harmonics implemented in the *SCALE3 ABSPACK* scaling algorithm were applied.[30] The structure was solved by direct methods and subsequently completed by difference Fourier recycling. Nonhydrogen atoms were refined anisotropically by using the full-matrix least-squares technique. Hydrogen atoms were found by difference Fourier synthesis after four cycles of anisotropic refinement, and refined as riding on the adjacent carbon atom with an individual isotropic temperature factor equal to 1.2 times the value

of equivalent temperature factor of the parent atom. Olex2[31] and SHELXS, SHELXL[32] programs were used for all the calculations.

(28) CCDC 1543174, 1543282, and 1543283 contains the supplementary crystallographic data for compounds **4a**, **4e**, and **6e**, respectively. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(29) **3′-(4-Isopropylphenyl)-1′*H*-spiro[cyclopentane-1,2′-quinazolin]-4′(3′*H*)-one** (**6b**)
Colorless crystals; yield: 907 mg (94%); mp 244–246 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.22 (d, J = 6.8, 6 H, CH$_3$), 1.43 (s, 2 H, CH$_2$), 1.71 (d, J = 7.6 Hz, 4 H), 1.89 (s, 2 H, CH$_2$), 2.91 (m, 1 H, CH), 6.71 (t, J = 7.2 Hz, 1 H, ArH), 6.86 (d, J = 8.0 Hz, 1 H, ArH), 6.93 (s, 1 H, NH), 7.10 (d, J = 8.0 Hz, 2 H, ArH), 7.28 (d, J = 7.6 Hz, 3 H, ArH), 7.67 (d, J = 7.2 Hz, 1 H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.2, 23.7, 32.9, 36.2, 81.6, 114.9, 115.6, 117.1, 126.5, 127.8, 129.7, 132.9, 136.1, 146.4, 147.4, 163.0. Anal. Calcd for C$_{21}$H$_{24}$N$_2$O (320.43): C 78.71, H 7.55, N 8.74; Found: C 79.26, H 7.89, N 9.03.

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