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An unexpected route toward the synthesis of spiro-benzo[*b*]acridine-furan derivatives

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ABSTRACT

A facile and straightforward procedure for the synthesis of spiro-benzo[*b*]acridine-6,2′-furan derivatives via the reaction between benzo[*b*]acridine-6,11-dione, electron-deficient acetylenic compounds, and an isocyanide is described. The benzo[*b*]acridine-6,11-dione is obtained from the reaction between 2-(aminomethyl)aniline and 2-hydroxynaphthalene-1,4-dione via an unexpected reaction pathway. The products are synthesized in medium to high yields and no complicated purification is required.

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Spiro compounds are of importance from a biological and pharmaceutical point of view and they show different activities such as antimycobacterial,[1] inhibition of the rabbit muscle 26S proteasome,[2] and act as an MDM2-p53 inhibitor providing a new and promising strategy toward cancer treatment.[3] Examples have been used effectively to treat different types of human tumor cells.[4] Some examples are active toward doxorubicin- and *cis*-platin-resistant human tumor cells, as reported by Gomez-Monterrey et al.[5] Modulation of the activity of p53 has also been reported. This behavior led to cell death which is crucial to inhibition of tumor development.[6] Anti-influenza A virus activity via modulation of the dynamic of the M2 proton channel has also been reported.[7] These compounds are promising replacements for amantadine which exhibits side effects on the central nervous system and due to increased drug resistance by the virus. Fungicidal,[8] antimalarial activity,[9] HIV-1 reverse transcriptase dimerization inhibitor properties,[10] and anticancer properties (including multi-drug resistant cancers)[11] have been reported for compounds containing this moiety. Spiro compounds are also important due to their interesting structural and physical properties. Bent ladder-type hexaphenylenes with spiro-linkages have been used as blue emitters.[12] Chiral and flexible metal-organic frameworks using bifunctional spiro linkers have been synthesized by Gedrich et al.[13] Some compounds with high T_g values have showed promising photo-physical properties and they are very good candidates for use in optoelectronics.[14] Phosphorescent organic light-emitting diodes (PHOLEDs) have also been synthesized based on spiro systems.[15]

As a result of the above-mentioned properties of spiro compounds, different methods for their synthesis have been introduced. For example, a synthesis via a one-pot, two-step, three-component reaction has been reported by Zhuang.[16] In addition, the use of $NiCl_2$ or $CoCl_2$ as the catalyst under microwave irradiation conditions,[17] Fischer carbene complexes,[18] ultrasound-assisted combinatorial synthesis,[19] organocatalytic approaches,[20] palladium-catalyzed synthesis,[21] a domino Knoevenagel/Michael/cyclization sequence catalyzed by cupreine,[22] Pd-catalyzed intramolecular *ipso*-Friedel–Crafts allylic alkylation of phenols,[23] domino Stetter-aldol–Michael and Stetter-aldol–Aldol reactions,[24] and other methods[25–28] have been reported.

As part of our studies on MCRs,[29–32] a procedure for the synthesis of pyran derivatives **5** via a two-step reaction between CH-acid **3**, dialkyl acetylenedicarboxylates [such as dimethyl acetylenedicarboxylate (DMAD)] and an isocyanide was designed. Initially, the possibility of the synthesis of compound **3** from the reaction of 2-(aminomethyl)aniline (**1**) and 2-hydroxynaphthalene-1,4-dione (**2**) in acetic acid at room temperature was examined. Analysis of the spectroscopic data led us to conclude that the desired product **3** was not obtained; instead the reaction proceeded via an unexpected route yielding compound **4**. With compound **4** in hand, the multicomponent reaction between active-carbonyl compound **4**, electron-deficient acetylenic compounds, and an isocyanide was examined (Scheme 1).

In a pilot experiment, benzo[*b*]acridine-6,11-dione (**4**), diethyl acetylenedicarboxylate (**7**, R = Et), and benzyl isocyanide (**8**,

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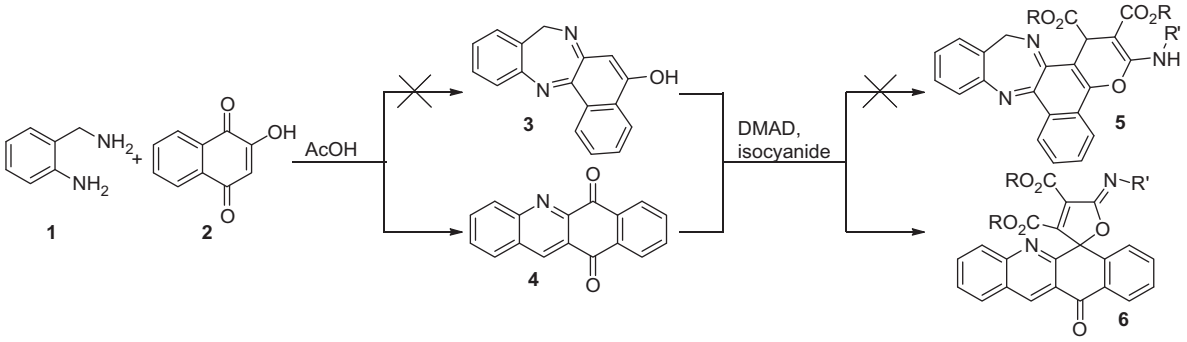
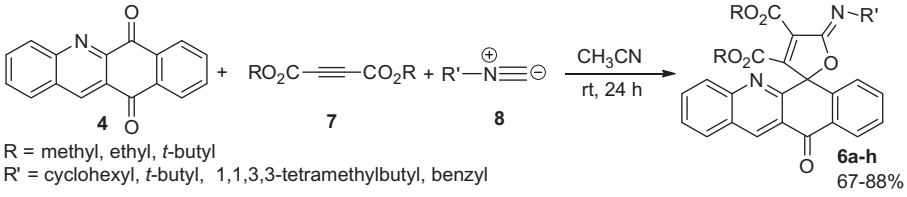


Scheme 1. Planned reaction for the synthesis of pyran derivatives versus the unexpected pathway toward the spiro-compounds.



Scheme 2. Synthesis of spiro-benzo[*b*]acridine-6,2′-furan derivatives.

R′ = Bn) in CH_3CN were stirred at room temperature for 24 h. After completion of the reaction, the precipitated product was separated by filtration, washed with *n*-hexane, and recrystallized from EtOH/H_2O to afford product **6a** in 88% yield. To explore the scope of this reaction, different electron-deficient acetylenic compounds and various alkyl, aryl, and alicyclic isocyanides were employed (Scheme 2) to afford a range of diverse spiro-benzo[*b*]acridine-6,2′-furans (Table 1).

The structures of the products were deduced from their IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data. As an example, the ^{1}H NMR spectrum of compound **6a** showed two triplets (J = 7.0 Hz) at 0.81 and 1.32 ppm for two CH_3 groups and two quartets at 3.82 and 4.40 ppm for two CH_2 moieties (J = 7.0 Hz). The protons of the N–CH_2 moiety were observed as an ABq pattern at 4.65 ppm and the aromatic protons and C=CH occurred at 7.22–8.40 and 9.34 ppm, respectively. The ^{1}H-decoupled ^{13}C NMR spectrum of **6a** showed 31 distinct resonances in agreement with the proposed structure. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. Finally, the structure of product **6a** was confirmed unambiguously by single-crystal X-ray analysis (Fig. 1).

Although the mechanistic aspects of the above-mentioned reaction for the synthesis of these spiro compounds have not been explored experimentally, a reasonable mechanism can be suggested (Scheme 3). The initial step involves the reaction between the electron-deficient acetylenic compound **7** with isocyanide **8** to produce the intermediate Huisgen zwitterion **9**. Attack of **9** on compound **4** leads to intermediate **10**, which after intramolecular cyclization, yields the desired products **6a–h**.

As mentioned previously, the designed reaction for the synthesis of compound **3** did not occur as expected and benzo[*b*]acridine-6,11-dione (**4**) was obtained instead via an unexpected pathway. Two suggested pathways for the formation of compound **4** are presented in Scheme 4. It is conceivable in route **I**, that the initial event is the formation of intermediate **12** by attack of compound **2** on 2-(aminomethyl)anilium salt **11**. In the next step, intermediate **15** is obtained by an intramolecular condensation reaction. In the case of pathway **II**, a hetero-Diels–Alder reaction between intermediate **13** and compound **2** produces the intermediate **14**, which after dehydration, affords dione **15**. Finally, the product **4** is obtained via oxidation of intermediate **15**.

To distinguish the preferred pathway (**I** or **II**), the reaction shown in Scheme 5 was run. Analysis of the reaction medium after 24 h showed that the desired product had been produced. This indicated that the reaction proceeded via a hetero-Diels–Alder mechanism to produce intermediate **17**, which underwent two successive oxidations in the reaction medium to produce the final product. This finding leads us to conclude that the preferred pathway to produce benzo[*b*]acridine-6,11-dione is via route **II**.

In summary, a simple and efficient synthetic procedure has been developed for the synthesis of functionalized spiro-benzo[*b*]acridine-6,2′-furan derivatives from readily available starting materials. The reported approach has advantages including a simple work-up, clean production of the products, and good functional group tolerance. As spiro-containing compounds possess biological activities, we hope the described procedure might be of interest to those seeking novel synthetic approaches for medicinal chemistry.

Preparation of benzo[*b*]acridine-6,11-dione (4)

To a magnetically stirred solution of 2-(aminomethyl)aniline (**1**) (0.12 g, 1 mmol) in AcOH (5 mL), was added 2-hydroxynaphthalene-1,4-dione (**2**) (0.34 g, 2 mmol). The reaction was stirred for 24 h and the precipitated product was separated by filtration and washed with distilled H_2O (10 mL). The product was obtained as a dark yellow powder (0.19 g, 73%); mp >270 °C. IR (KBr) cm^{-1}: 1688, 1665, 1616, 1578, 1489, 1380, 1345. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.84–8.42 (8H, m, H-Ar), 9.31 (1H, s, CH). ^{13}C NMR (62.90 MHz, DMSO-d_6) δ: 27.4, 28.3, 29.8, 54.6, 83.7, 83.8, 124.5, 126.8, 127.6, 127.7, 128.7, 128.9, 129.3, 130.5, 130.6, 131.0, 133.7, 135.5, 137.9, 138.7, 149.4, 153.9, 182.3. MS m/z: 259 (M^+, 100), 231 (74), 203 (72), 176 (19), 150 (8), 127 (10), 101 (28), 76 (37), 50 (22). Anal. Calcd for $C_{17}H_9NO_2$: C, 78.76; H, 3.50; N, 5.40. Found: C, 78.72; H, 3.40; N, 5.36.

Table 1
Synthesized spiro-benzo[*b*]acridine-6,2′-furan derivatives

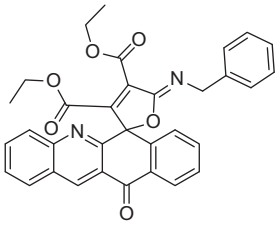
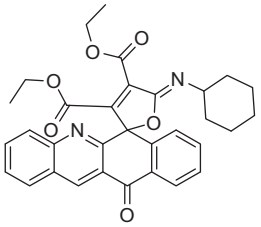
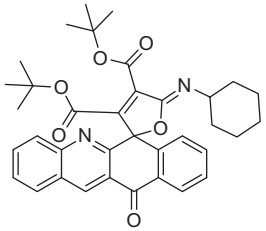
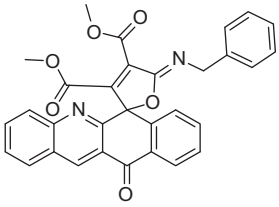
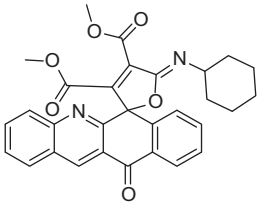
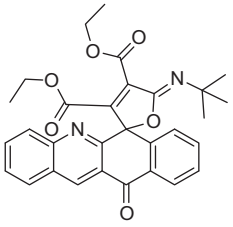
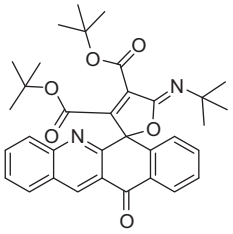
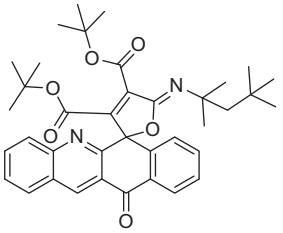
Entry	R	R′	Product	Yield (%)
6a	Et	Bn		88
6b	Et	Cyclohexyl		67
6c	*t*-Bu	Cyclohexyl		73
6d	Me	Bn		70
6e	Me	Cyclohexyl		75
6f	Et	*t*-Bu		80
6g	*t*-Bu	*t*-Bu		84

Table 1 (*continued*)

Entry	R	R′	Product	Yield (%)
6h	*t*-Bu	1,1,3,3-Tetramethylbutyl		79

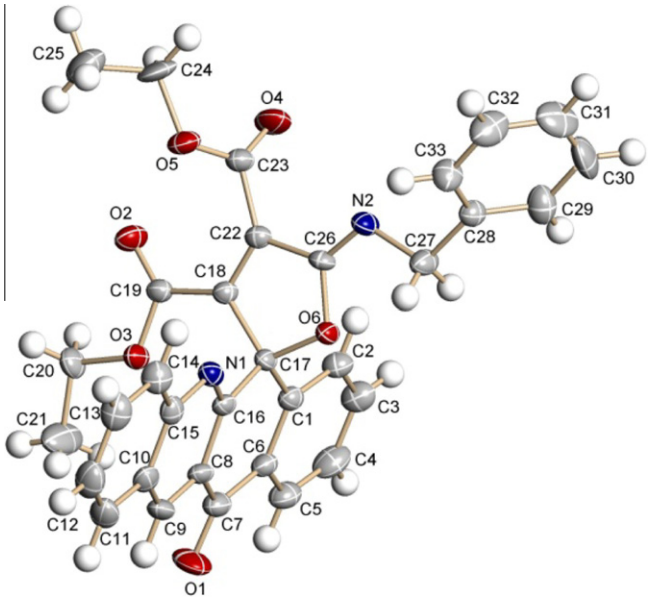
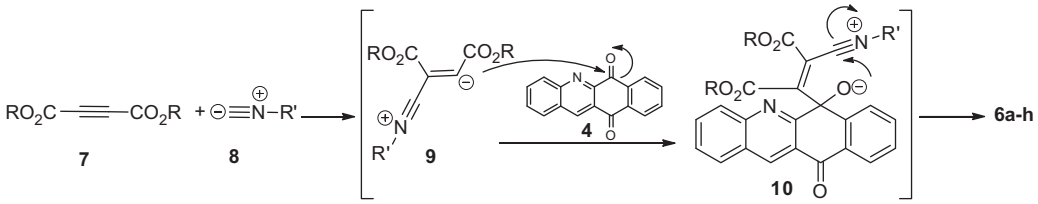


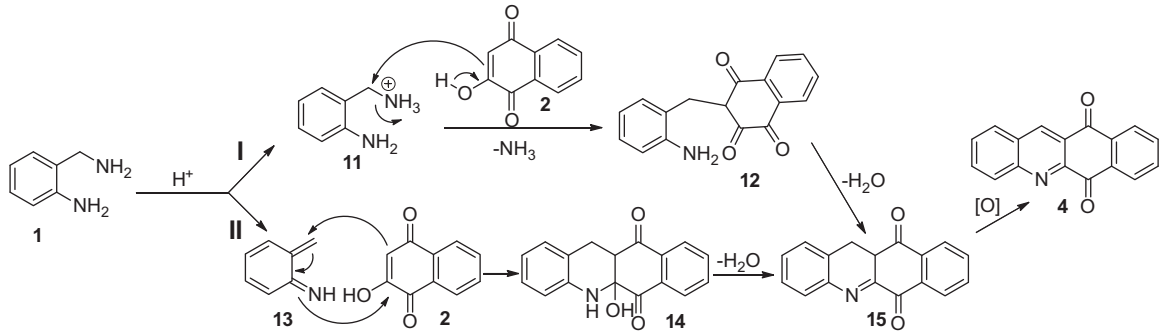
Figure 1. ORTEP diagram of product **6a** (CCDC 871537).

Preparation of diethyl 5′-(benzylimino)-11-oxo-5′*H*,11*H*-spiro[benzo[*b*]acridine-6,2′-furan]-3′,4′-dicarboxylate (6a); typical procedure

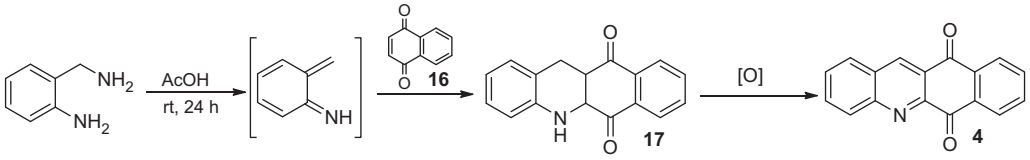
To a magnetically stirred solution of benzo[*b*]acridine-6,11-dione (**4**) (0.26 g, 1 mmol) in CH_3CN (10 mL), was added diethyl acetylenedicarboxylate (0.17 g, 1 mmol) and benzylisocyanide (0.12 g, 1 mmol). The resulting mixture was stirred at room temperature for 24 h. After completion of the reaction (monitored by TLC), the precipitated product was separated by filtration, washed with *n*-hexane (5 mL), and recrystallized from EtOH/H_2O (3/2) to afford the desired product as a yellow powder (0.48 g, 88%); mp 157–158 °C. IR (KBr) cm^{-1}: 3443, 3058, 3033, 2975, 2892, 1731, 1671, 1591, 1495, 1457, 1376, 1339. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.81 (3H, t, J = 7.0 Hz, O–CH_2CH_3), 1.32 (3H, t, J = 7.0 Hz, O–CH_2CH_3), 3.82 (2H, q, J = 7.0 Hz, O–CH_2CH_3), 4.40 (2H, q, J = 7.0 Hz, O–CH_2CH_3), 4.65 (2H, AB_q, J = 15.2 Hz, N–CH_2), 7.22–8.40 (13H, m, H-Ar), 9.34 (1H, s, CH). ^{13}C NMR (100.64 MHz, DMSO-d_6) δ: 9.3, 10.1, 47.4, 58.3, 58.6, 81.8, 120.3, 122.9, 123.5, 123.7, 123.8, 124.5, 124.6, 124.8, 125.1, 126.4, 126.8, 129.7, 131.5, 132.3, 133.3, 134.0, 135.3, 141.3, 145.0, 150.2, 154.0, 155.2, 157.3, 177.9, 202.7. MS *m/z*: 546 (M^+, 8), 441



Scheme 3. Suggested mechanism for the synthesis of spiro-benzo[*b*]acridine-6,2′-furan derivatives **6a**–**h**.



Scheme 4. Proposed pathways for the synthesis of benzo[*b*]acridine-6,11-dione (**4**).



Scheme 5. Reaction used to distinguish the pathway of the reaction to give compound **4**.

(16), 413 (28), 368 (28), 340 (25), 313 (26), 296 (28), 269 (46), 238 (32), 117 (28), 91 (100). Anal. Calcd for $C_{33}H_{26}N_2O_6$: C, 72.52; H, 4.79; N, 5.13. Found: C, 72.60; H, 4.80; N, 5.03.

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