EFFICIENT PROTOCOL FOR THE SYNTHESIS OF NOVEL SPIRO[acenaphthylene-1,2'-pyrrolidin]-2-one COMPOUNDS

Yan Lin, Zhijie Fu, Tianhua Shen, Fengfeng Che, and Qingbao Song
College of Chemical Engineering, Zhejiang University of Technology, Hangzhou, China

GRAPHICAL ABSTRACT

Abstract An efficient catalyst-free synthesis of 3'-benzoyl-4',5'-diphenyl-2H-spiro [acenaphthylene-1,2'-pyrrolidin]-2-one derivatives via one-pot 1,3-dipolar cycloaddition of acenaphthenquinone, arylmethyl amines, and chalcones with high regioselectivity is described. The structure of the cycloadducts were characterized by infrared, high-resolution mass spectrometry (electrospray ionization), 1H NMR, and 13C NMR spectra, and the structure of 4a was confirmed using x-ray single-crystal structure analysis.

Keywords [3+2]-Cycloaddition; acenaphthenquinone; arylmethyl amine; chalcone; spiropyrrolidine

INTRODUCTION

Spirocyclic compounds containing five-membered rings represent a significant class of natural products characterized by a wide range of biological activities.[1] The key step to achieve such skeleton is the construction of the five-membered ring, especially nitrogen-containing five-membered heterocycles. Among numerous strategies, the intermolecular [3 + 2] cycloaddition is regarded to be a straightforward one.[2] Generally, azomethine ylides would react with electron-deficient olefinic dipolarophiles to form nitrogen-containing five-membered rings. This kind of
reaction is highly desirable in terms of efficiency and selectivity. A lot of protocols have been developed for the generation of azomethine ylides, including the ring opening of aziridines, the desilylation of various silylamino derivatives, the decarboxylation condensation of amino acids, the 1,2-prototropy/metallo-azomethine ylides of amino-acid-derived imines, and the deprotonation of iminium salts.[3] Recently, the azomethine ylides generated in situ by the reaction of isatins or acenaphthenequinone with amino acids have been reported widely, which provide possibilities for tandem cyclizations.[4]

On the other hand, chalcone is a kind of aromatic ketone that forms the central skeleton for a number of useful biologically active products.[5] They have been reported to possess numerous important properties, including antioxidant, antifungal, anti-inflammatory, antimicrobial, and anticancer activities.[6] The incorporation of the chalcone moiety in the target products is expected to enhance their biological properties. In continuation of our research on the synthesis of spirocyclic compounds,[7] we herein develop a catalyst-free, three-component, one-pot reaction to construct 3'-benzoyl-4',5'-diphenyl-2H-spiroacenaphthylene-1,2'-pyrrolidin]-2-one derivatives, which includes the initial reaction of acenaphthenequinone and terminal amides to form azomethine ylides and the following intermolecular [3 + 2] cycloaddition with chalcones (Scheme 1).

RESULTS AND DISCUSSION

Initially, the reaction of acenaphthenequinone 1, benzylamine 2a, and chalcone 3a was chosen as the model reaction. By simply stirring the starting reagents in ethanol under reflux condition for 90 min, the desired 3'-benzoyl-4',5'-diphenyl-2H-spiroacenaphthylene-1,2'-pyrrolidin]-2-one 4a was obtained in good yield (Table 1, entry 1). Then, a variety of solvents were tested, and the best yield was observed in ethanol (Table 1, entries 2–10). When the reaction was carried out in water, no product was detected due to the insolubility of starting materials (Table 1, entry 10). With temperature decreases, the yields of 4a were obviously reduced (Table 1, entries 11–13).

With the optimal reaction conditions established, this protocol was applied to a series of arylmethyl amines and chalcones to obtain the corresponding spiro-compounds 4 in a regiocontrolled manner. As summarized in Table 2, chalcones bearing electron-withdrawing groups or electron-donating groups could afford the corresponding products in good to excellent yields. This cycloaddition is regioselective with the electron-rich carbon of the dipole attacking the β-carbon of the α, β-unsaturated moiety of 3. To our delight, the [3 + 2] cycloaddition affords a racemic mixture exclusively, despite the presence of four stereocenters and eight possible racemates in the products as found in many similar cycloaddition studies.[8] The
Table 1. Optimization of reaction conditions$^a$

| Entry | Solvent     | Temp. (°C) | Yield$^b$ (%) |
|-------|-------------|------------|---------------|
| 1     | EtOH        | 78         | 89            |
| 2     | 1,4-Dioxane | 101        | 75            |
| 3     | AcOEt       | 77         | 69            |
| 4     | THF         | 66         | 63            |
| 5     | Toluene     | 110        | Trace         |
| 6     | CH$_3$CN    | 80         | 77            |
| 7     | CH$_3$OH    | 65         | 82            |
| 8     | n-PrOH      | 97         | 87            |
| 9     | n-BuOH      | 117        | 85            |
| 10    | H$_2$O      | 100        | NR            |
| 11    | EtOH        | 20         | 45            |
| 12    | EtOH        | 40         | 67            |
| 13    | EtOH        | 60         | 73            |

$^a$Reactions were performed with acenaphthenequinone 1 (0.5 mmol), benzylamine 2a (0.5 mmol), chalcone 3a (0.5 mmol), and solvents (5 mL).

$^b$Isolated yield.

Table 2. Synthesis of spiro[acenaphthylene-1,2'-pyrrolidin]-2-one derivatives$^a$

![Chemical Structure]

| Entry | Ar$^1$ | Ar$^2$ | Ar$^3$ | 4 | Yield (%)$^b$ |
|-------|--------|--------|--------|---|---------------|
| 1     | C$_6$H$_5$ | C$_6$H$_5$ | C$_6$H$_5$ | 4a | 89            |
| 2     | C$_6$H$_5$ | 2-NO$_2$-C$_6$H$_5$ | C$_6$H$_5$ | 4b | 68            |
| 3     | C$_6$H$_5$ | 4-NO$_2$-C$_6$H$_5$ | C$_6$H$_5$ | 4c | 84            |
| 4     | C$_6$H$_5$ | 4-F-C$_6$H$_5$ | C$_6$H$_5$ | 4d | 76            |
| 5     | C$_6$H$_5$ | 4-Cl-C$_6$H$_5$ | C$_6$H$_5$ | 4e | 80            |
| 6     | C$_6$H$_5$ | 4-Br-C$_6$H$_5$ | C$_6$H$_5$ | 4f | 92            |
| 7     | C$_6$H$_5$ | 4-I-C$_6$H$_5$ | C$_6$H$_5$ | 4g | 91            |
| 8     | C$_6$H$_5$ | 4-CH$_3$-C$_6$H$_5$ | C$_6$H$_5$ | 4h | 67            |
| 9     | C$_6$H$_5$ | 4-OCH$_3$-C$_6$H$_5$ | 2,4-Cl$_2$-C$_6$H$_4$ | 4i | 79            |
| 10    | C$_6$H$_5$ | 4-OCH$_3$-C$_6$H$_5$ | 4-Br-C$_6$H$_4$ | 4j | 87            |
| 11    | C$_6$H$_5$ | C$_6$H$_5$ | 4-NO$_2$-C$_6$H$_4$ | 4k | 83            |
| 12    | C$_6$H$_5$ | C$_6$H$_5$ | 4-Cl-C$_6$H$_4$ | 4l | 84            |
| 13    | C$_6$H$_5$ | C$_6$H$_5$ | 4-Br-C$_6$H$_4$ | 4m | 89            |
| 14    | C$_6$H$_5$ | C$_6$H$_5$ | 4-CH$_2$-C$_6$H$_4$ | 4n | 71            |
| 15    | C$_6$H$_5$ | C$_6$H$_5$ | 4-OCH$_3$-C$_6$H$_4$ | 4o | 75            |
| 16    | C$_6$H$_5$ | C$_6$H$_5$ | C$_{10}$H$_7$ | 4p | 80            |
| 17    | 4-Cl-C$_6$H$_4$ | C$_6$H$_5$ | C$_6$H$_5$ | 4q | 82            |
| 18    | 4-OCH$_3$-C$_6$H$_4$ | C$_6$H$_5$ | C$_6$H$_5$ | 4r | 69            |
| 19    | 2-Br-C$_6$H$_4$ | C$_6$H$_5$ | C$_6$H$_5$ | 4s | 86            |
| 20    | C$_3$H$_7$O | C$_6$H$_5$ | C$_6$H$_5$ | 4t | 78            |
| 21    | C$_3$H$_7$N | C$_6$H$_5$ | C$_6$H$_5$ | 4u | 93            |

$^a$Reaction of acenaphthenequinone 1, arylmethylenamines 2, and chalcones 3 in ethanol reflux for 90 min.

$^b$Isolated yield.
regioselective outcome of the spiroacenaphthylene-1,2'-pyrrolidin]-2-one derivatives 4 was confirmed by using infrared (IR), high-resolution mass spectrometry (HRMS) [electrospray ionization (ESI)], $^1$H NMR, and $^{13}$C NMR spectra, and the structure of 4a was confirmed using x-ray single-crystal structure analysis (Fig. 1).

For example, the IR spectrum of 4a showed an absorption peak at 3317 cm$^{-1}$, which was assigned to the N–H bond of pyrrolidine ring, and two absorption peaks at 1702 and 1685 cm$^{-1}$, indicating the carbonyl groups of acenaphthenone and benzoyl, respectively. The $^1$H NMR spectrum of 4a displayed a doublet at $\delta = 5.25$ ppm for Hc, a doublet at $\delta = 4.89$ ppm for Ha, and a triplet at $\delta = 4.42$ ppm for Hb. The value of $\delta$ (Hb) is smaller than $\delta$ (Hc) because the electron-withdrawing effect of nitrogen atom is stronger than that of benzoyl. The NH proton of the pyrrolidine ring appeared as a broad singlet at $\delta = 2.80$ ppm. The $^{13}$C NMR spectrum of 4a showed a peak at $\delta = 72.4$ ppm, which was assigned to the spiro-carbon. The signals at $\delta = 208.4$ and 197.8 ppm confirmed the presence of acenapthenone and benzoyl carbonyl carbons, respectively. Moreover, the presence of a molecular ion peak at $m/z$ 480.1967 [M+H]$^+$ in the HRMS spectrum confirmed the formation of 4a (calculated for 4a C$_{34}$H$_{26}$NO$_2$[M+H]$^+$: 480.1964).

In the molecule of chalcone, due to the electron-withdrawing effect of benzoyl group, the $\beta$-carbon is more electrophilic than the $\alpha$-carbon. Therefore, the $\beta$-carbon is the preferred position for a nucleophilic attack by carbanion of the azomethine ylides. This clearly indicated the regioselective outcome of product 4a. Another reason may be the unfavorable steric interactions between the carbonyl group of acenaphthenone moiety and the benzoyl of dipolarophile.[9]

A plausible mechanism for the synthesis of spiroadducts 4 is proposed in Scheme 2. The reaction of acenaphthenequinone 1 with arylmethyl amines 2 led to the formation of the azomethine ylides 5, which served as dipoles. The carbanion of azomethine ylides 5 then attacked the electrophilic $\beta$-carbon of chalcones in a concerted manner; the products 4 were obtained because of electronic effect and steric-hindrance effect.

Figure 1. ORTEP diagram of 4a.
CONCLUSIONS

In conclusion, we have developed a simple one-pot protocol for the facile synthesis of functionalized spiro[acenaphthylene-1,2'-pyrrolidin]-2-one derivatives via 1,3-dipolar cycloaddition of the azomethine ylides with chalcones. The reactions were carried out under mild conditions without using catalysts and possess the advantages of high atom efficiency and wide substrate scopes. All cycloadducts were obtained in a highly regioselective manner and were characterized by IR, HRMS (ESI), $^1$H NMR, and $^{13}$C NMR spectra, and the structure of 4a was confirmed by x-ray single-crystal structure analysis.

EXPERIMENTAL

$^1$H NMR spectra and $^{13}$C NMR spectra were recorded on a Bruker Avance III 500-MHz spectrometer, using CDCl$_3$ as solvent (500 MHz for $^1$H or 126 MHz for $^{13}$C, respectively). IR spectra (KBr) were recorded on a Nicolet 6700 spectrometer. Melting points were taken on Büchi M-560 apparatus in open capillary tubes and are uncorrected. HRMS were carried out on Decay-60000 LCQ Deca XP. X-ray crystallographic intensity data were collected using a Bruker Smart Apex II instrument. The reaction mixtures were monitored by thin-layer chromatography (TLC) on silica-gel plates (60 F-254). All chemicals were purchased from Aladdin (Shanghai, China) chemical company.

General Procedure for the Synthesis of Chalcones 3

A solution of 0.01 mol of aryl aldehyde and 0.01 mol of acetophenone in 10 mL of ethanol was taken in a 25-mL flask equipped with a magnetic stirring bar. To this solution, 10 mL of 2 M NaOH solution was added with the help of a dropping funnel while keeping the flask in an ice-water bath. Then, the reaction mixture was stirred
for 4–5 h at room temperature; subsequently the crude product was filtered and recrystallized from ethanol.

**General Procedure for the Preparation of Spiro[acenaphthylene-1,2'-pyrrolidin]-2-ones 4**

A mixture of acenaphthenequinone 1 (0.5 mmol), arylmethyl amine 2 (0.5 mmol), and chalcone 3 (0.5 mmol) in ethanol (5 mL) was stirred at reflux for 90 min, as indicated by TLC. After completion of the reaction, the mixture was cooled to room temperature. Then the precipitate formed in the reaction mixture was filtered and recrystallized from ethanol to obtain the pure product.

**3’-Benzoyl-4’,5’-diphenyl-2H-spiro[acenaphthylene-1,2'-pyrrolidin]-2-one (4a)**

Yellow powder; mp 218–220 °C; IR (KBr, ν, cm⁻¹): 3317, 3060, 1707, 1685, 1601, 1281, 783, 699; ¹H NMR (500 MHz, CDCl₃) δ 7.89 (dd, J = 7.5, 2.2 Hz, 2H), 7.64 (t, J = 7.1 Hz, 2H), 7.58 (dt, J = 7.2, 5.1 Hz, 2H), 7.51 (d, J = 7.4 Hz, 2H), 7.43 (d, J = 7.1 Hz, 2H), 7.31–7.28 (m, 4H), 7.26–7.17 (m, 2H), 7.13 (d, J = 7.3 Hz, 2H), 7.00 (t, J = 7.4 Hz, 1H), 6.82 (t, J = 7.8 Hz, 2H), 5.25 (d, J = 10.5 Hz, 1H, Hc), 4.89 (d, J = 10.5 Hz, 1H, Ha), 4.42 (t, J = 10.5 Hz, 1H, Hb), 2.80 (s, 1H). ¹³C-NMR (126 MHz, CDCl₃) δ 208.4, 197.8, 141.5, 140.7, 139.3, 139.1, 136.9, 132.1, 131.8, 131.2, 129.9, 128.7, 128.5, 128.3, 127.9, 127.7, 127.6, 127.2, 127.1, 126.9, 124.8, 122.8, 121.7, 72.4, 68.4, 62.7, 55.7. HRMS (ESI): Calculated for C₃₄H₂₆NO₂[M+H]⁺: 480.1964; found: 480.1967.

**SUPPLEMENTAL MATERIAL**

Supplemental data for this article can be accessed on the publisher’s website.

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