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Synthesis of 2-Benzylidene-3-Pyrrolines and Their Synthetic Transformation

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Abstract: A series of benzylidene-3-pyrrolines were prepared from chalcone derivatives, arylacetylene and sulfonamide via a three-step sequence without the isolation of intermediates. Typically, the reaction of 1,3-di-*p*-tolylprop-2-en-1-one with lithium phenylacetylide was followed by substitution with tosylamide and then silver-catalyzed *5-exo-dig* cyclization to give *N*-tosyl-2-benzylidene-3,5-di-*p*-tolyl-2,5-dihydro-1*H*-pyrrole with a 86% yield. Furthermore, transformation to the corresponding substituted 3-pyrrolin-2-one and pyrrole by *m*-chloroperbenzoic acid (mcpba)-oxidation and acid-catalyzed aromatization, respectively, was investigated.

Keywords: pyrrole; benzylidene-3-pyrroline; γ-lactam

1. Introduction

Both pyrrole and pyrroline are five-membered nitrogen-containing heterocycles, representing an important class of the privileged scaffolds occurring in nature [1–3] and pharmaceuticals [4–8]. A few examples of their biological activity are shown in Figure 1. Although the synthetic methods leading to pyrrole and/or pyrroline rings are well-documented, there is still a demand for developing new approaches for highly substituted and functionalized compounds.

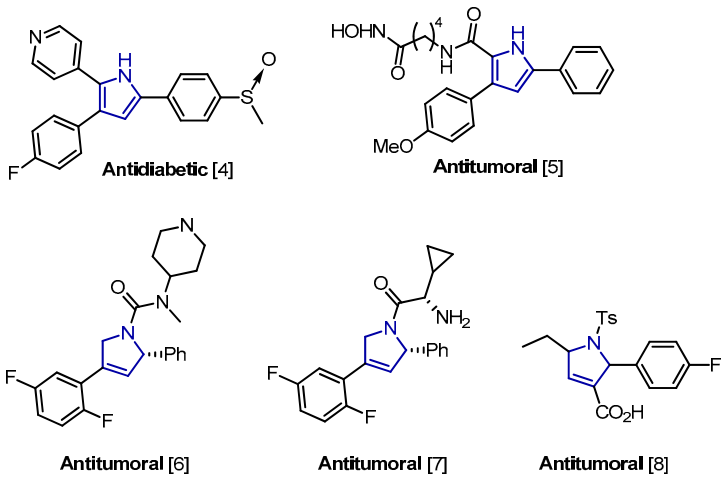


Figure 1. Selected pyrrole and pyrroline compounds with their biological activities.

In this context, 3-ylidene-1-pyrrolines (**I**) have received much attention, because of the presence of an exocyclic double bond, a reactive imine bond and a nucleophilic nitrogen site on the ring [9]. Thus, various transformations of these compounds leading to pyrrole derivatives have been disclosed.

On the other hand, 2-ylidene-3-pyrrolines (**II**), isomeric structures of **I** (when R″ = H), are less explored [10–12]. Quite a few reports show that 2-ylidene-3-pyrrolines are reactive intermediates and undergo aromatization upon heating to render the corresponding pyrroles [13]. In this work, we would like to investigate the possibility of the cyclization of (*Z*)-2-en-4-yn-1-amines (**III**) to give 2-ylidene-3-pyrroline and then their further transformation.

2. Materials and Methods

2.1. Materials and Instrumentation

All chemicals were purchased and used without any further purification. Flash chromatography was performed using a silica gel 230–400 mesh. Nuclear magnetic resonance spectra were recorded in $CDCl_3$ or acetone-d_6 on either a Bruker AM-300 or AVANCE 400 spectrometer (Bruker BioSpin Corporation, Billerica, MA, USA). Chemical shifts are given in parts per million relative to Me_4Si for ^1H and $^{13}C\{^1H\}$ NMR. Infrared spectra were measured on a Nicolet Magna-IR 550 spectrometer (Series-II) (Spectralab, ON, Canada) as KBr pellets, unless otherwise noted.

2.2. Synthesis

A solution of 2.5 M *n*-butyllithium (0.4 mL, 1.0 mmol) was added to a solution of phenylacetylene (1.0 mmol) in tetrahydrofuran (THF, 4 mL) at the temperature of a dry-ice/acetone bath. Chalcone (0.4 mmol) in pre-dried THF (2 mL) was slowly added to the above solution. After addition, the reaction mixture was heated to reflux for 4 h. Upon cooling, ether (10 mL) was added and the mixture was washed with saturated ammonium chloride solution and water. The organic portion was dried over magnesium sulfate and concentrated under reduced pressure. The crude product **2** was subjected to the next step.

A solution of toluenesulfonamide (1.2 mmol) and sulfuric acid (60 µL, 1.2 mmol) in THF (2 mL) was warmed to 50 °C. The crude **2** from the last step in THF (0.5 mL) was slowly added to the above solution and kept at 50 °C for several hours. Ether (10 mL) was then added, and the mixture was washed with saturated sodium hydrogen carbonate solution and water. The organic portion was dried over magnesium sulfate and concentrated under reduced pressure to give crude product **3**.

Compound **3** from the last step was dissolved in dichloromethane (2 mL), and $Ag(CH_3COO)$ (6.7 mg, 0.04 mmol) and triphenylphosphine (10.5 mg, 0.04 mmol) in methanol (2 mL) were then added to the above solution slowly. After addition, the mixture was heated at 60 °C for several hours. Upon cooling, the solution was concentrated to give the crude products, which were chromatographed on silica gel with the elution of dichloromethane/hexane to give the final pure product.

2.3. Spectroscopic Characterization

Compound **4a** was obtained as a yellow powder (168.9 mg, 86%): mp 92–94 °C; ^1H NMR (400 MHz, CD_3COCD_3): δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 2H), 7.43–7.39 (m, 4H), 7.25–7.14 (m, 9H), 6.40 (s, 1H), 6.00 (d, *J* = 1.7 Hz, 1H), 5.76 (d, *J* = 1.8 Hz, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 145.1, 143.7, 142.7, 139.2, 138.4, 137.7, 137.2, 134.7, 130.8, 130.4, 130.3, 130.2, 130.2, 130.1, 129.3, 128.9, 128.4, 127.9, 119.4, 71.1, 21.5, 21.3, 21.2; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd. for $C_{32}H_{30}NO_2S$: 492.1992, found 492.1991.

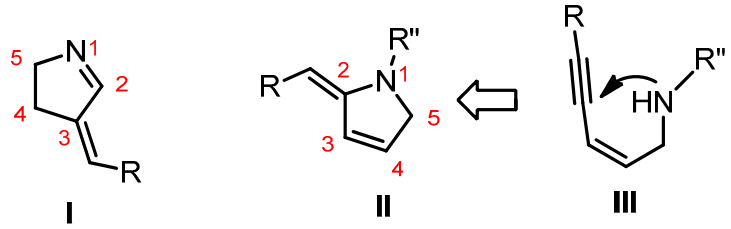
All spectral data of other compounds are deposited in the Supplementary Materials.

3. Results and Discussion

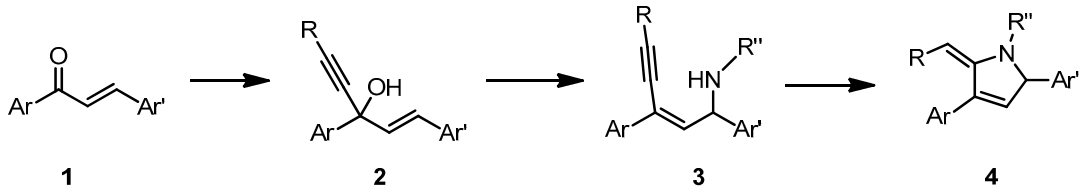
3.1. Synthetic Design

The synthetic scheme leading to the target molecule **4** is illustrated in Scheme 1. In order to have 2-en-4-ynilamine (**3**) for the cyclization study, we envision that the S_N2' substitution of 1-en-4-yn-3-ol (**2**) with a nitrogen nucleophile would be a good approach, because **2** is readily available from the

addition of acetylide with a chalcone molecule **1** (Scheme 2). Another important advantage of this approach is that the starting chalcone compounds are commercially available or prepared by aldol condensation reactions.



Scheme 1. Structure of ylidene-pyrrolines.



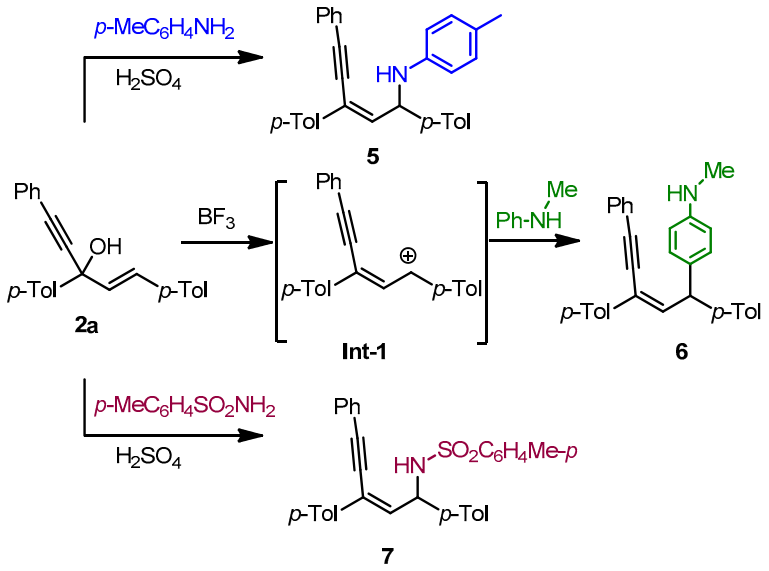
Scheme 2. Our synthetic approach.

3.2. Optimization of Each Step

Our ultimate goal is to carry out this three-step reaction sequentially without the isolation and purification of products in each step. However, it is necessary to have optimized reaction conditions for each step. Accordingly, the first step in preparing compound **2a** (R = C_6H_5; Ar = Ar′ = *p*-$CH_3C_6H_4$-) is achieved by the addition of an equal molar amount of acetylide anion to a solution of **1a** (Ar = Ar′ = *p*-$CH_3C_6H_4$-) in THF at the temperature of a dry-ice/acetone bath. A simple workup by extraction gave **2a** with a quantitative yield.

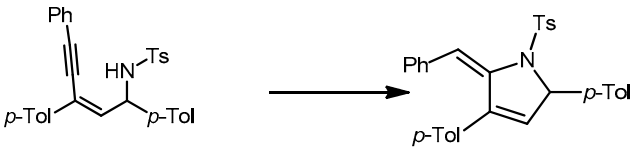
The substitution of **2a** with various nitrogen nucleophiles was then investigated, and it appears to be a challenge (Scheme 3). When *p*-toluidine was used as the nucleophile, the substrate was consumed within a few hours in the presence of 30 mol% of H_2SO_4, but the desired product **5** was obtained in trace amounts. Interestingly, the use of *N*-methylaniline as the reagent gave an electrophilic aromatic substitution product, **6**. Obviously, the carbocation intermediate **int-1** produced via the acid-promoted dissociation of **2a** follows the electrophilic substitution with the aromatic ring instead of a combination with the nitrogen donor of *N*-methylaniline. Finally, the treatment of **2a** in a THF solution with *p*-toluenesulfonamide in the presence of sulfuric acid at 50 °C gave the desired substitution product **7**, quantitatively.

With compound **7** in hand, the cyclization reaction leading to the desired product under various catalytic conditions was examined (Table 1). As shown in the table, it was revealed that silver ion is a suitable catalyst for promoting the cyclization, and the best reaction condition is carrying out the reaction in the presence of triphenylphosphine ligand in a mixed solvent at 60 °C (Table 1, entry 6). It is observable that the use of phosphine ligand readily assists the catalytic cyclization. Presumably, the triphenylphosphine ligand is able to stabilize the intermediate and diminish the decomposition of the metal complex. The reaction proceeds via a *5-exo-dig* cyclization, instead of a *6-endo-dig* pathway, to yield the five-membered ring product.



Scheme 3. Nucleophilic displacement of **2a** with amine derivatives.

Table 1. Optimization of cyclization reaction [1].



7 Ts = *p*-$MeC_6H_4SO_2$- **4a**

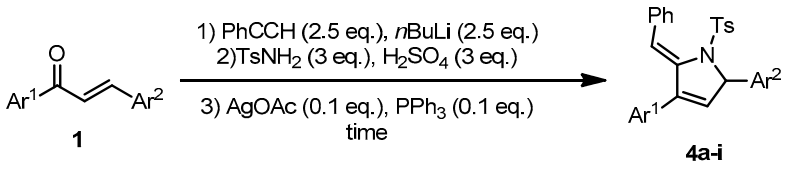
Entry	Catalyst (eq.)	Solvent [2]	Temp.	Time (h)	Yield of 4a [2]
1	$Pd(OAc)_2$ (0.1)	DCM	rt	24	0%
2	$PdCl_2$ (0.1)/*t*BuOK (1.0)	toluene	50 °C	24	0%
3	AgOAc (0.1)/PPh_3 (0.1)	DCM/MeOH	rt	24	23%
4	AgOAc (0.1)	DCE/MeOH	60 °C	2	26%
5	AgOAc (0.1)/PPh_3 (0.1)	DCE/MeOH	60 °C	2	65%
6	AgOAc (0.1)/PPh_3 (0.1)	DCE/MeOH	60 °C	3	100% (86%) [3]
7	AgOAc (0.1)/P(*o*Tol)$_3$ (0.1)	DCE/MeOH	60 °C	2	57%
8	AgOAc (0.1)/$P(OPh)_3$ (0.1)	DCE/MeOH	60 °C	2	0%
9	AgOAc (0.1)/dppe (0.05)	DCE/MeOH	60 °C	2	44%

[1] Reaction conditions: **7** (0.2 mmol) and catalyst in solvent. dppe = $PPh_2CH_2CH_2PPH_2$; DCM = dichloromethane; DCE = 1,2-dichloroethane. eq. = equivalent; rt = room temperature. [2] NMR yields. [3] Isolated yield given in parentheses.

3.3. Reaction Scope

With the understanding of the reaction conditions of each step, a sequential process without the purification of the product of each step was attempted, and compound **4a** was chosen as the target. As described in detail in Section 2.2, compound **4a** was obtained with an 86% isolated yield. Thus, various substituted chalcones were subjected to this reaction sequence accordingly, to render the expected products with good-to-excellent yields (Table 2). All the compounds obtained were characterized by NMR and mass analyses, and the structure of **4a** was further confirmed by X-ray crystallography (Figure S1).

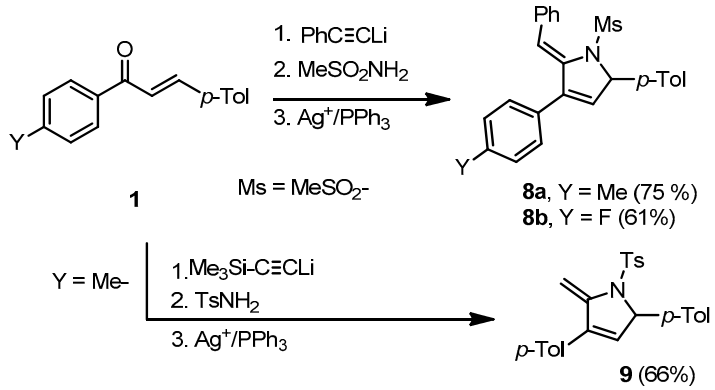
Table 2. Reaction scope [1].



Entry	Substituents	Time	Product (Yield)
1	Ar^1 = *p*-MeC_6H_4-; Ar^2 = *p*-MeC_6H_4-	4 h	**4a** (86%)
2	Ar^1 = *p*-$MeOC_6H_4$-; Ar^2 = *p*-MeC_6H_4-	25 h	**4b** (42%)
3	Ar^1 = *p*-FC_6H_4-; Ar^2 = *p*-MeC_6H_4-	22 h	**4c** (81%)
4	Ar^1 = *p*-ClC_6H_4-; Ar^2 = *p*-MeC_6H_4-	22 h	**4d** (70%)
5	Ar^1 = *p*-BrC_6H_4-; Ar^2 = *p*-MeC_6H_4-	22 h	**4e** (55%)
6	Ar^1 = *p*-MeC_6H_4-; Ar^2 = *p*-FC_6H_4-	46 h	**4f** (71%)
7	Ar^1 = *p*-MeC_6H_4-; Ar^2 = *p*-ClC_6H_4-	66 h	**4g** (61%)
8	Ar^1 = *o*-MeC_6H_4-; Ar^2 = *p*-MeC_6H_4-	4 h	**4h** (72%)
9	Ar^1 = *p*-MeC_6H_4-; Ar^2 = 1-naphthyl	22 h	**4i** (64%)

[1] Reaction conditions: (1) A mixture of PhC≡CH (1 mmol) and *n*-BuLi (1 mmol) was added to **1** (0.4 mmol) in THF at −78 °C. After 4 h, water extraction gave the crude product **2**. (2) $TsNH_2$ (1.2 mmol) and H_2SO_4 (1.2 mmol) were added to a solution of crude product **2** in THF for 4 h. An aqueous NH_4Cl solution workup gave the crude product **3**. (3) To crude **3** in DCE were added AgOAc (0.04 mmol) and PPh_3 (0.04 mmol) in methanol. The mixture was heated at 60 °C. Workup and purification by chromatography yielded the desired product.

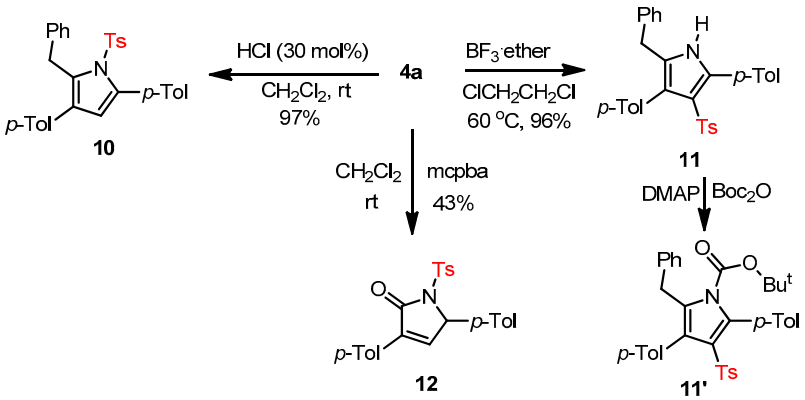
Instead of *p*-toluenesulfonamide, methanesulfonamide is also a good nitrogen nucleophile for the reaction. Two examples of the mesylated products **8a**–**b** are illustrated in Scheme 4. In addition, trimethylsilylacetylene is also suitable for this sequential reaction to give **9** as the single product. It is noticed that the trimethylsilyl group was removed under the reaction conditions (Scheme 4).



Scheme 4. Additional scope of the reactions.

3.4. Further Synthetic Transformation

Next, we studied the synthetic application of the obtained 2-ylidene-3-pyrrolines (Scheme 5). As expected, in the presence of acid, compound **4a** readily underwent C=C double migration to give the corresponding pyrrole compound **10** at room temperature. Presumably, the driving force for this double bond migration comes from the aromaticity of the pyrrole ring. When the reaction was carried out with the use of BF_3 as the acid catalyst at 60 °C, the pyrrole compound **11** was still formed with a 96% yield according to NMR determination. However, it is observable that the migration of the tosyl group to the 3-position of the ring occurred to yield the tosyl-substituted pyrrole **11** [14,15]. Compound **11** was treated with Boc_2O in the presence of a base to give *N*-Boc-protected pyrrole **11'**, which crystallized to give a single crystal form for X-ray analysis. Thus, crystallographic determination confirmed the structure of **11**, i.e., the 3-position of the tosyl group in the ring. The oxidation of **4a** with mcpba (*m*-chloroperbenzoic acid) produced the α,β-unsaturated γ-lactam **12** with a reasonable yield.



Scheme 5. Synthetic transformation of 2-ylidene-3-pyrrolines.

4. Conclusions

In this study, we succeeded in the preparation of 2-ylidene-3-pyrrolines via a three-step reaction without the purification of intermediates. In addition, the synthetic transformation of these compounds into the corresponding pyrrole, tosyl-substituted pyrrole and α,β-unsaturated γ-lactam was demonstrated. This development offers a synthetic approach to producing highly substituted pyrrole derivatives, which are useful for further application.

Supplementary Materials: The following are available online at http://www.mdpi.com/2624-781X/1/2/5/s1. Spectral data of all products, Crystallography of **4a** and **11′**, Figure S1: ORTEP plot of **4a** (30% probability ellipsoids), Figure S2: ORTEP plot of **11′** (30% probability ellipsoids), Table S1: Bond distances and bond angles of **4a**, Table S2: Bond distances and bond angles of **11′**.

Author Contributions: Conceptualization, S.-T.L.; methodology, investigation and data collection, M.-T.H.; crystallography, Y.-H.L.; writing—original draft preparation, S.-T.L.; writing—review and editing, M.-T.H. and S.-T.L.; supervision, S.-T.L.; funding acquisition, S.-T.L. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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