Consecutive Isomerization and Cyclization of 3-(2-Aminophenyl)-1-arylprop-2-yn-1-ols Leading to 2-Arylquinolines in the Presence of Potassium Hydroxide

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Received October 9, 2003

3-(2-Aminophenyl)-1-arylprop-2-yn-1-ols are readily converted to 2-arylquinolines in good yields in ethanol at 80° in the presence of potassium hydroxide *via* domino isomerization and cyclization.

J. Heterocyclic Chem., **41**, 409 (2004).

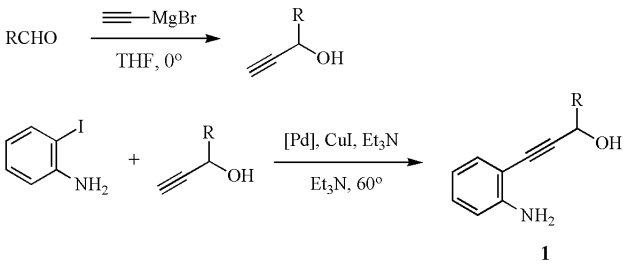
Introduction.

Isomerization has been extensively studied to achieve efficient and straightforward reactions in organic synthesis. In connection with this report, it is known that several transition metals such as Pd [1], Ru [2], Rh [3] and Ir [4] isomerize propargylic alcohols to enones or enals [5]. In addition to these reports, Minn and Kundu have reported that 2-iodopyrimidines and 6-iodouracils are coupled with propargylic alcohols to give 3-heteroaryl substituted enones under Sonogashira coupling conditions [6]. However, to the best of our knowledge, although substrates are restricted, it was firstly reported by Cacchi that alkyl 4-hydroxy-2-alkynoates and 4-hydroxy-2-alkyn-1-ones were isomerized to alkyl 4-oxo-2-alkenoates and 1,4-dioxo-2-alkenes, respectively in the presence of only tributylamine [7]. Recently, Müller and Saito have further disclosed the isomerization of propargylic alcohols to enones under triethylamine or triton B [8] On the other hand, a clear-cut example for the synthesis of cyclic compounds using this isomerization protocol seems to be limited to the synthesis of 3,5-disubstituted 2-pyrazolines [8a] and ruthenium-catalyzed synthesis of butyrolactone [9] and pyrroles [10]. Prompted by these circumstances, we have directed our attention to the application of this isomerization to the synthesis of N-heterocycles. Herein we report a base-mediated consecutive isomerization and cyclization of 3-(2-aminophenyl)-1-arylprop-2-yn-1-ols leading to 2-arylquinolines.

Results and Discussion.

The starting 3-(2-aminophenyl)-1-arylprop-2-yn-1-ols **1** are easily available by the known procedures shown in Scheme 1. Aldehydes are treated with ethynylmagnesium bromide to give propargylic alcohols [11] that are then subjected to react with 2-iodoaniline under Sonogashira coupling conditions to afford **1** [12]. Several reactions with 3-(2-aminophenyl)-1-phenylprop-2-yn-1-ol (**1a**, **1**: R = Ph) under various conditions were carried out to obtain a satisfying yield of 2-phenylquinoline (**2a**, **2**: R = Ph) (Scheme 2). Our initial study was performed in the presence of a transition metal catalyst since transition metal-catalyzed redox isomerizations of propargyl alcohols to α,β-unsatuarted carbonyl compounds are known [1-4]. When **1a** was subjected under the conditions of $RuCl_2(PPh_3)_3$ (2 mol%)/80°/5 hours/dioxane, **2a** was not produced at all and almost all **1a** was recovered unchanged [13]. Treatment of **1a** at a higher reaction temperature (180°) under similar conditions afforded **2a** in only 5% yield. These results indicate that a ruthenium catalytic system was not effective for the present reaction. However, the addition of equimolar amount of KOH to the conditions of $RuCl_2(PPh_3)_3$ (2 mol%)/80°/2 hours/dioxane afforded **2a** in 72-78% yields (several runs) [14]. Eventual reaction conditions excluded the presence of a ruthenium catalyst from the system. Among the solvents we examined, ethanol in terms of product **2a** yield revealed to be the solvent of choice (83%; dioxane, 65%; toluene, 54%).

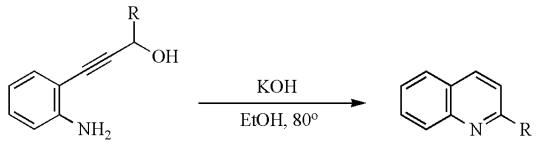
Scheme 1



1

Having established reaction conditions, various **1** were screened in order to investigate the reaction scope, and several representative results are summarized in Table 1. With 1-arylpropargylic alcohols (**1a**-**1j**) the isomerization-cyclization products were formed in the range of 62-89% yields (runs 1-10). The product yield was not significantly

Scheme 2



1 2

affected by the electronic nature of the substituent on the aromatic ring attached to carbon bearing OH of **1a**-**1j**, whereas the position of that had some relevance to the product yield (runs 2-4). In the reaction with 3-(2-aminophenyl)-1-(2-methylphenyl)prop-2-yn-1-ol (**1b**), a longer reaction time was necessary for the effective formation of 2-(2-methylphenyl)quinoline (**2b**) (run 2). The reaction proceeds likewise with heteroarylpropargylic alcohols (**1k**-**1m**) to afford the corresponding 2-heteroaryl substituted quinolines (**2k** and **2l**) in good yields (runs 11-12). However, in the case of 3-(2-aminophenyl)-1-methylprop-2-yn-1-ol (**1m**) the reaction resulted in several unidentifiable compounds without the formation of 2-methylquinoline (**2m**) and an intermediate (see Scheme 3).

Table 1

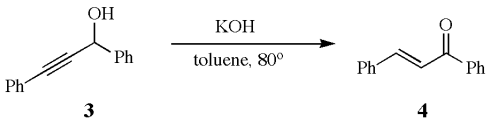
Consecutive Isomerization and Cyclization of **1** Leading to **2** [a]

Run	**1**	Quinoline **2**	Isolated yield
1	**1a** R = Ph	**2a**	83
2	**1b** R = 2-MeC_6H_4	**2b**	46 (62 [b])
3	**1c** R = 3-MeC_6H_4	**2c**	73
4	**1d** R = 4-MeC_6H_4	**2d**	80
5	**1e** R = 4-MeOC_6H_4	**2e**	72
6	**1f** R = 3-MeOC_6H_4	**2f**	83
7	**1g** R = 2-MeOC_6H_4	**2g**	73
8	**1h** R = 4-FC_6H_4	**2h**	89
9	**1i** R = 4-ClC_6H_4	**2i**	86
10	**1j** R = 3,4-$(MeO)_2C_6H_3$	**2j**	65
11	**1k** R = 2-furanyl	**2k**	35
12	**1l** R = 2-thienyl	**2l**	67
13	**1m** R = Me	**2m**	0

[a] Reaction conditions: **1** (0.5 mmol), KOH (0.5 mmol), EtOH (2 mL), 80° (bath temperature) for 7 hours; [b] For 20 hours.

As to the reaction pathway, although no intermediates were obtained, this seems to proceed *via* an initial isomerization of propargylic alcohol moiety of **1** to α,β-unsaturated carbonyl compound followed by cyclodehydration to give **2**. It is known that this isomerization can be rationalized by the formation of an allenol intermediate under a base [7,8] and a transition metal-catalyzed intramolecular transfer hydrogenation [1-4]. We confirmed, in a separate experiment, that 1,3-diphenylprop-2-yn-1-ol (**3**) was readily isomerized to *trans*-chalcone (**4**) in the presence of KOH (Scheme 3) in 70% yield with concomitant formation of several unidentifiable compounds.

Scheme 3



3 4

In summary, we have demonstrated that 3-(2-aminophenyl)-1-arylprop-2-yn-1-ols undergo consecutive isomerization and cyclization in the presence of KOH to afford 2-arylquinolines in good yields. The present reaction is a novel example leading to a cyclic compound using a base-mediated isomerization of propargylic alcohols to enones.

EXPERIMENTAL

^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using Me_4Si as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting points apparatus and are uncorrected. The isolation of pure products was carried out *via* thin layer (silica gel 60 GF_{254}, Merck) chromatography. Commercially available organic and inorganic compounds were used without further purification except for the solvent, which was distilled by standard methods before use.

General Procedure for Consecutive Isomerization and Cyclization of 3-(2-Aminophenyl)-1-arylprop-2-yn-1-ols **1** Leading to 2-Arylquinolines **2**.

A mixture of 3-(2-aminophenyl)-1-arylprop-2-yn-1-ol (0.5 mmol) and KOH (28 mg, 0.5 mmol) in EtOH (2 mL) was placed in a 5 mL screw-capped vial and allowed to react at 80° for 7 hours. The reaction mixture was filtered through a short silica gel column (ethyl acetate-chloroform mixture). Removal of the solvent left a crude mixture, which was separated by TLC (ethyl acetate-hexane mixture) to give 2-arylquinolines. Except for **2f**, **2g**, **2i** and **2j**, all products are noted in our recent report [13g].

2-(3-Methoxyphenyl)quinoline (**2f**).

This compound was obtained as a solid, mp 110° (petroleum ether) (lit [15] mp 108-110°); ^1H NMR ($CDCl_3$): δ 3.90 (s, 3H), 7.00 (dd, J = 2.5 and 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.48-7.51 (m, 1H), 7.68-7.72 (m, 2H), 7.77-7.83 (m, 3H), 8.15-8.18 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 55.8, 113.1, 115.8, 119.5, 120.4, 126.7, 127.7, 127.9, 130.0, 130.1, 130.2, 137.2, 141.6, 148.6, 157.5, 160.6.

2-(2-Methoxyphenyl)quinoline (**2g**).

This compound was obtained as a pale yellow oil, (lit [16] viscous oil); ^1H NMR ($CDCl_3$): δ 3.82 (s, 3H), 7.00 (dd, J = 8.0 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.84-7.88 (m, 2H), 8.11 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 55.6, 111.4, 121.2, 123.4, 126.1, 127.0, 127.4, 129.0, 129.2, 129.3, 129.4, 130.6, 131.5, 135.1, 148.3, 157.2.

2-(4-Chlorophenyl)quinoline (**2i**).

This compound was obtained as a solid, mp 111-112° (hexane) (lit [17] mp 112°); ^{1}H NMR ($CDCl_3$): δ 7.46-7.53 (m, 3H), 7.69-7.73 (m, 1H), 7.77-7.80 (m, 2H), 8.08-8.18 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 118.5, 126.5, 127.2, 127.5, 128.8, 129.0, 129.7, 129.8, 135.5, 136.9, 138.0, 148.2, 155.9.

2-(3,4-Dimethoxyphenyl)quinoline (**2j**).

This compound was obtained as a solid, mp 116° (hexane) (lit [18] mp 116-117°); ^{1}H NMR ($CDCl_3$): δ 3.96 (s, 3H), 4.05 (s, 3H), 6.99-7.01 (m, 1H), 7.48-7.53 (m, 1H), 7.65-7.74 (m, 2H), 7.80-7.88 (m, 3H), 8.14-8.20 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 56.0, 56.1, 110.4, 111.0, 118.6, 120.2, 126.0, 127.0, 127.4, 129.5, 129.6, 132.5, 136.7, 148.2, 149.4, 150.4, 156.9.

Procedure for Isomerization of 1,3-Diphenylprop-2-yn-1-ol (**3**) to *trans*-Chalcone (**4**).

A mixture of 1,3-diphenylprop-2-yn-1-ol (62 mg, 0.3 mmol) and KOH (17 mg, 0.3 mmol) in toluene (2 mL) was placed in a 5 mL screw-capped vial and allowed to react at 80° for 1 hour. The reaction mixture was filtered through a short silica gel column (ethyl acetate-chloroform mixture). Removal of the solvent left a crude mixture, which was separated by TLC (ethyl acetate/hexane = 1/10) to give *trans*-chalcone (44 mg, 70%).

Acknowledgment.

The present work was supported by Korea Research Foundation Grant (KRF-2002-070-C00055). C.S.C. gratefully acknowledges a MOE-KRF Research Professor Program (KRF-2001-050-D00015).

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