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ORIGINAL PAPER

One-Pot Formation of Functionalized Indole and Benzofuran Derivatives Using a Single Bifunctional Ruthenium Catalyst

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Abstract We report a single bifunctional ruthenium catalyst for cyclization of terminal alkynylaryl amines and -phenols to corresponding indole and benzofuran derivatives in good yields. Key features the ability to cyclize and hydrate terminal alkynes in one step and to deuterate the heteroaromatic compounds formed.

Keywords Bifunctional · Indole · Benzofuran · Cyclize · Hydrate · Deuteration

1 Introduction

Terminal alkynes can be activated by isomerizing them on metal centers to form metal vinylidene complexes [1]. These are usually sufficiently electrophilic for nucleophilic attack by water [2], alcohol [3, 4], phenols [5], amines [6, 7] and many other nucleophiles. A wide variety of transition metal based catalysts have been reported to catalyze alkyne hydration [8], alkynylaryl amine [9–15] and -phenol [16–19] cyclization, etc. However, there has not been any report, to the best of our knowledge, of one catalyst capable of carrying out cyclization and hydration in the same reaction flask. Here we present our single bifunctional ruthenium catalyst which possesses a unique set of applications: cyclization, hydration and deuteration to synthesize a variety of functionalized heteroaromatic compounds.

Our group reported a bifunctional catalyst for terminal alkyne hydration [20] in 2004. During the study of the substrate scope it was found that sulfonamide protected alkynyl amine **2** cyclized to hemiaminal **3** (Scheme 1) which on further heating eliminated water to give enamine derivative **5**. We have also reported mechanistic studies of alkyne hydration [21], which so far confirm the attack of water on the intermediate vinylidene. Therefore, we envisioned that our catalyst could generate an intermediate aldehyde which in the presence of a tethered amine or phenol, could lead to cyclization. N and O heterocycle synthesis would then be easily possible via dehydration. Our initial attempts to perform cycloisomerization reactions of homopropargylic alcohols [22] led to the conclusion that our ruthenium phosphine complexes formed carbene complexes which did not readily turn over to give required enol ethers as products. We then focused on the reactions of *o*-alkynylaryl amines and -phenols with a variety of functional groups on the nitrogen atom as well as the aromatic ring to give different substituted indole and benzofuran derivatives, as shown in Table 1 [23]. Eventually we realized that the catalyst has two potential applications—(1) *anti*-Markovnikov alkyne hydration and (2) terminal alkyne cyclization to give heteroaromatic compounds. The studies of our catalyst on bis alkyne substrates and the ability to deuterate is presented.

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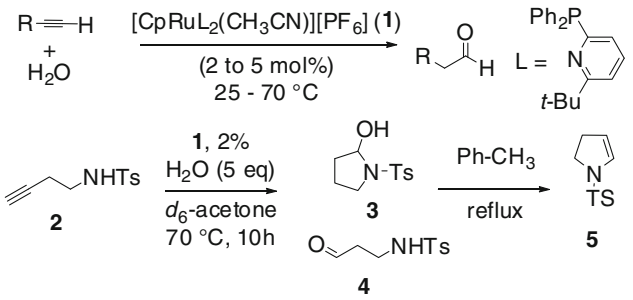
2 Experimental

Example of procedure for one-pot cyclization and hydration—synthesis and isolation of 18 (Scheme 2): To a scintillation vial containing a stir bar was added **12** (0.0350 g, 0.224 mmol), **1** (0.0111 g, 0.011 mmol), H_2O (0.0206 g, 1.121 mmol) and acetone (3.0 mL). The cap was then closed and the vial was heated at 70 °C for 10 h. After confirming the completion of the reaction by TLC the



Scheme 1 General bifunctional catalyst for alkyne hydration

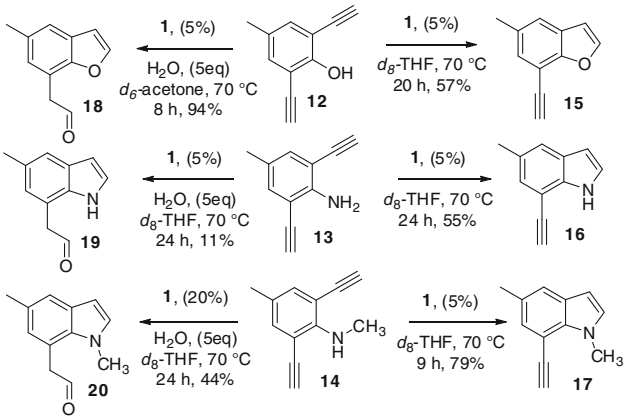
Table 1 Results of cyclization

Substrate	Product	Time (h)	Yield (%)
6	9	96	80
7	10	17	99
8	11	2	99

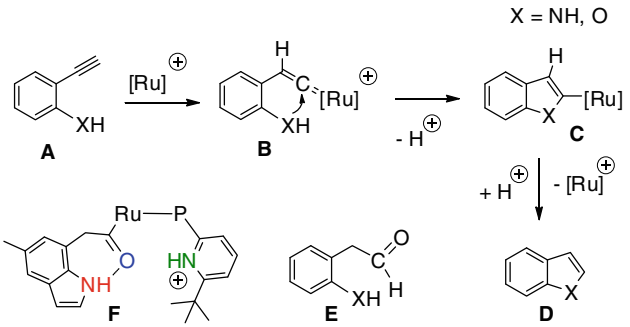
solvents were evaporated by rotary evaporation. The residue was extracted with pentane and the solvent was once again evaporated to give **18** as a pale yellow solid (0.0280 g, 74%). ^{1}H NMR (d_8-THF, 400 MHz) δ 9.71 (t, $J = 2.4$ Hz, 1H), 7.70 (d, $J = 2.4$ Hz, 1H), 7.31 (s, 1H), 6.97 (s, 1H), 6.75 (d, $J = 2.4$ Hz, 1H), 3.85 (d, $J = 2.0$ Hz, 1H), 2.40 (s, 1H); ^{13}C NMR (d_8-THF, 100 MHz) 197.8, 153.4, 146.4, 133.4, 128.8, 127.6, 120.9, 117.1, 107.4, 45.1, 21.3; FT-IR (KBr, cm^{-1}) 3111.8, 2922.9, 2831.9, 2360.7, 1719.6, 1538.4, 1470.9, 1206.6, 1137.2, 1032.6, 761.7, 730.6; HRMS calcd for $C_{11}H_{10}O_2$: 174.0676, found: 174.0675. For anhydrous conditions the reaction was performed in dry and deoxygenated THF.

3 Results and Discussion

Scheme 2 summarizes the studies towards one pot cyclization and hydration studies. When **12** was subjected to catalytic conditions in d_8-THF it gave **15** (20 h, 57%) based on NMR integrations. It was also noted that the reaction was faster in d_6-acetone. However traces of the aldehyde **18** were also seen due to the trace amount of water present in d_6-acetone.

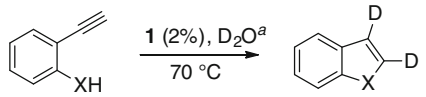


Scheme 2 One pot cyclization and hydration reactions; all yields determined using NMR integrations



Scheme 3 Probable mechanism

With this in mind the cyclization–hydration reaction was done in d_6-acetone and resulted in the formation of **18** (8 h, 94%). The success of these reactions led us to try other nitrogen analogues wherein cyclization of **13** under anhydrous conditions yielded **16** (20 h, 75%). Strangely though the subsequent hydration reaction was slow, giving after 24 h only 11% of **19**, with much of **16** (55%) remaining. Our hypothesis for this can be understood from Scheme 3, where the indole NH must play a role; in putative intermediate **F**, hydrogen bonding of the pyridinium moiety to the acyl could be precluded by competitive interaction with the indole NH. Consistent with this, not only did *N*-methylated substrate **14** cyclize to indole derivative **17** (9 h, 79%), but also hydration (forming **20**) was more facile, though 20 mol% catalyst was necessary. Also noted during the cyclization of substrate **14** was that the Cp peak for the catalyst was observed at 4.51 ppm in ^{1}H NMR and the corresponding ^{31}P signal for the same was at 43.5 ppm. During the course of the reaction the integral value of the Cp peak (^{1}H NMR, 4.52 ppm) decreased whereas a new Cp peak was observed (^{1}H NMR, 5.12 ppm and ^{31}P, 43.7 ppm). This signal corresponded to a catalytically inactive species which has been observed in previous mechanistic studies of alkyne hydration.



7, X = NH **7-d_3**, X = ND, 100% of theory (95%) at C1-C3
8, X = O **8-d_2**, X = O, 100% of theory (80%) at C2 and C3

[a] 5 equiv for **7**, in [D_6]acetone, 1 h; 28 equiv for **8**, in [D_8]THF, 68 h.

Scheme 4 Synthesis of polydeuterated indole and benzofuran

Finally we focused our attention on synthesis of deuterated heterocycles (Scheme 4). Previous attempts to make deuterated indoles required the NH to be protected [24–26]. It has still been difficult to deuterate both 2 and 3 positions of these heterocycles, and in fact 2,3-d_2-benzofuran is unknown. Our studies showed that using D_2O instead of H_2O, allowed the incorporation of deuterium at the 2 and 3 positions in significantly high yields. For this, substrates **7** and **8** were subjected to alkyne hydration conditions in presence of D_2O. Results showed that percent deuteration at each of the possible sites depended on the molar ratio of deuterium present in the reaction mixture, but in each case was 100% of the amount theoretically possible at each position. Control experiments were also performed on indole and benzofuran to study if there was any evidence of H/D exchange with D_2O itself or in the presence of **1**. For this indole and benzofuran were dissolved (in separate J. Young tubes) in d_6-acetone and 30 equivalents of D_2O was added followed by heating (70 °C, 1 h) the J. Young tube and monitoring the reaction by ^1H NMR. Subsequently, **1** (2 mol%) was added and the heating was continued over a period of 6 days. Under these conditions the NH hydrogen of indole was the only site susceptible to H/D exchange but there was no notable H/D exchange at positions 2 and 3 of either indole or benzofuran.

We have shown that the alkyne hydration catalyst is versatile in its synthetic application. Not only is it applicable in the synthesis of aldehydes but also in one pot cyclization and hydration yielding an aldehyde at position 7 of these heteroaromatic compounds. This has high synthetic utility as these aldehydes can lead to isoprene units which are known to exist in a variety of biologically active natural products. Also shown is the easy access to deuterated compounds with just a change of the nucleophile from H_2O to D_2O at otherwise not easy positions. Other synthetic applications of this catalyst in cyclization reactions are also in process.

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