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Convenient, DBU-promoted anti-Markovnikov hydration of 2-methyl-1-(3-arylprop-2-yn-1-yl)-1*H*-imidazoles in wet NMP

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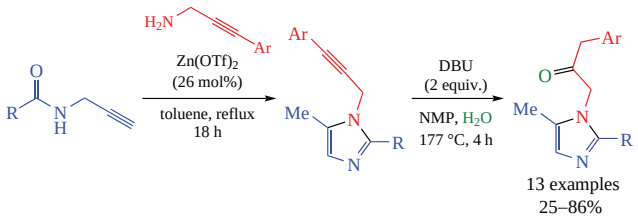
During attempts to involve 5-methyl-2-phenyl-1-(3-phenylprop-2-yn-1-yl)-1*H*-imidazole in a base-promoted, allene-mediated cyclization of the alkyne moiety onto the nearby aromatic ring, substantial amount of the ketone resulting from hydration of the alkyne with adventitious water was discovered. The formation of the ketone of the anti-Markovnikov alkyne hydration was developed into a preparative method. This method, alternative to the common acid- and metal-catalyzed approaches, may be of particular utility when alkyne hydration needs to be performed in the presence of acid-labile groups.



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Intramolecular reactions involving a carbon–carbon triple bond and an aromatic moiety are a proven way to build polycyclic (hetero)aromatic systems.[1] Although considered a 'red flag' in modern drug discovery in light of the ongoing quest for 'non-flatness' of ideal molecular scaffold for drug design,[2] polycyclic aromatics are often associated with interesting photophysical properties.[3] Nitrogen-containing polyheterocycles are frequently exploited as ligands for metal complexes.[4] As drugs, such compounds are of use in cancer treatment as they interact with DNA through intercalation and π-stacking and halt cancer cell hypertranscription (*cf.* naturally occurring base pair intercalators dactinomycin and doxorubicin as well as topoisomerase inhibitor camptothecin).[5] Recently, we were studying DBU-promoted cyclization of 5-methyl-2-phenyl-1-(3-phenylprop-2-yn-1-yl)-1*H*-imidazole **1a** inspired by the preparation of key intermediate **2** in the synthesis of alkaloid tylophorine,[6] a process thought to proceed *via* an allenic intermediate (Figure 1).[7] However, the desired cyclization to give tricycle **3a** (not a subject of the present communication) was persistently accompanied by the formation of difficult-to-separate ketone **4a**, formally the product of anti-Markovnikov hydration of the alkyne moiety in **1a** by adventitious water in NMP (*N*-methyl-2-pyrrolidone) and/or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). Ketones like **4a** have proven to be indispensable in the synthesis of muscarinic acetylcholine receptor antagonists,[8] radioactive technetium complexes for biomedical imaging[9] and anticancer aziridine natural products.[10] Alkyne hydration had never been brought about through such a simple, one-step protocol under basic conditions. According to the literature, Lewis acidic metal-catalyzed protocols[11] or two-step approach involving acidic hydrolysis[10] are typically employed, and often a directing group[12] needs to be strategically placed within the substrate to ensure anti-Markovnikov regiospecificity. However, methods to hydrate alkynes in the presence of acid-labile groups are of obvious value. Thus, we became interested in making the conversion **1a** → **4a** a productive process and exploring its generality. Herein, we report our achieving the said goals.

By intentionally adding water (2 equiv.) into the reaction mixture prior to adding DBU (2 equiv.) and heating to 177 °C, we achieved the full conversion of **1a** in 4 h and the formation of **4a** as a sole major product (in addition to several unidentified minor side products, TLC data). Product **4a** was isolated by chromatography in satisfactory 50% yield. Not intending to conduct extensive optimization, we conducted a brief variation in the quantity of DBU and the temperature regimens. It turned out that lowering the temperature to 100 °C as well as cutting DBU amount resulted in the full conversion not achieved even after 48 h of heating, at which point multiple new side-products were observed. Much faster conversion but a similar outcome in terms of the side product formation was observed at NMP reflux temperature. Therefore, we deemed the initially identified conditions, namely, DBU (2 equiv.), H_2O (2 equiv.), NMP, 177 °C, 4 h, to be optimal and proceeded to conduct the survey of 1-(3-arylylprop-2-yn-1-yl)-5-methyl-2-R-1*H*-imidazoles **1** as substrates for the newly discovered DBU-promoted anti-Markovnikov hydration of the 3-aryl propargylic moiety.

Starting substrates **1a**–**m** were synthesized from *N*-propargyl amides **5** through hydroamination with amines **6** followed by

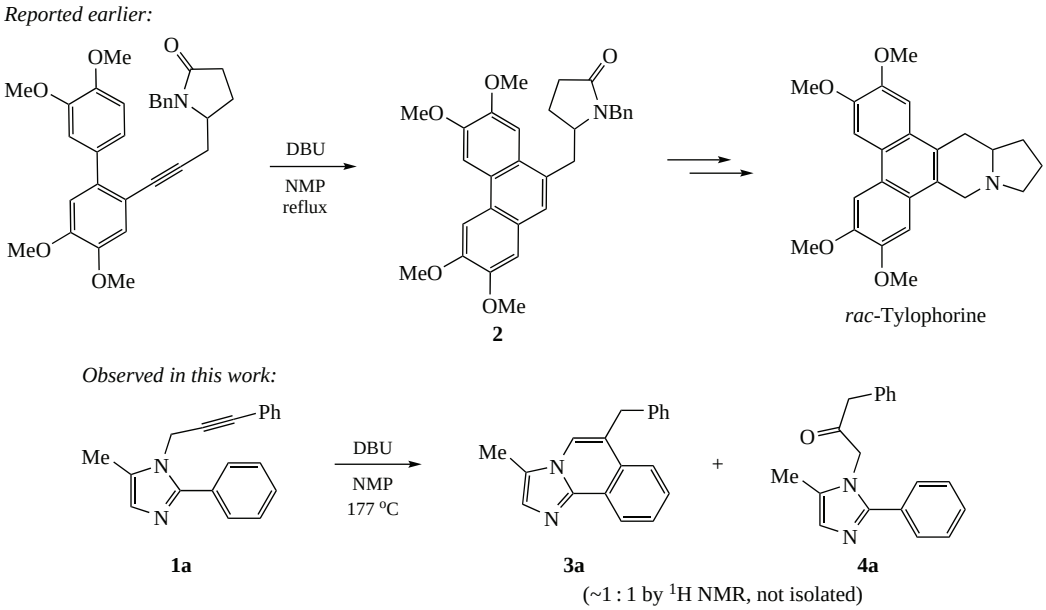
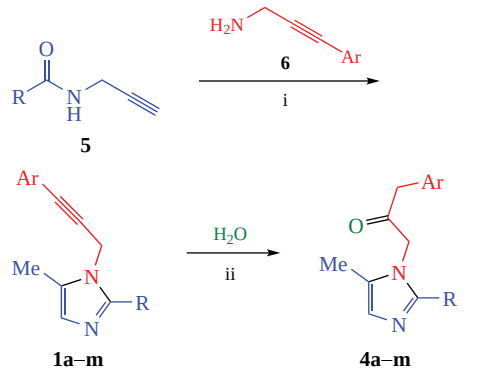


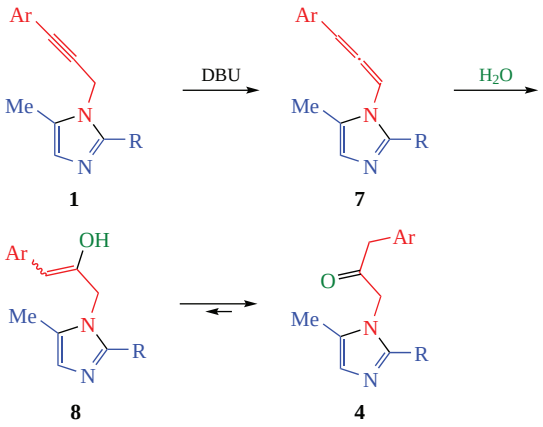
Figure 1 Background to the discovery of the reaction of DBU-promoted hydration of 5-methyl-2-phenyl-1-(3-arylprop-2-yn-1-yl)-1*H*-imidazoles.



a R = Ar = Ph (58/50)
b R = 4-BrC_6H_4, Ar = Ph (40/86)
c R = Ph, Ar = 2-MeC_6H_4 (79/29)
d R = Ph, Ar = 1-naphthyl (80/47)
e R = Bn, Ar = Ph (40/38)
f R = 2-furyl, Ar = Ph (10/46)
g R = 2-thienyl, Ar = Ph (60/64)
h R = Cy, Ar = Ph (79/25)
i R = *c*-C_5H_9, Ar = Ph (56/50)
j R = *c*-C_4H_7, Ar = Ph (38/50)
k R = *c*-C_3H_5, Ar = Ph (80/63)
l R = Me, Ar = Ph (41/44)
m R = 1-adamantyl, Ar = Ph (29/40)

Parentheses stand for yields (%) at stages i/ii, respectively

Scheme 1 *Reagents and conditions*: i, $Zn(OTf)_2$ (26 mol%), PhMe, reflux, 18 h; ii, DBU (2 equiv.), NMP, H_2O, 177 °C, 4 h.



Scheme 2

cycloaromatization (Scheme 1). The reaction was conducted in refluxing toluene and catalyzed by zinc triflate as described by Beller.[13,14] The yields of compounds **1a**–**m** were from disappointingly low (particularly in the case of 2-furyl derivative **1f**, perhaps due to lability of the furan ring under the reaction's forcing conditions) to quite high (compounds **1c**,**d**,**h**,**k**). Compounds **1a**–**m** were then treated with DBU in wet NMP (see Scheme 1) as described above to furnish anti-Markovnikov hydration products **4a**–**m** in modest to good yields after chromatographic purification (for detailed procedures, see Online Supplementary Materials).

Mechanistically, the transformation **1** → **4** likely involves the formation of allenic intermediate **7**. The latter undergoes hydration to form conjugated enol **8**, which defines the observed anti-Markovnikov regiospecificity. Enol **8** would tautomerize to observed ketone **4** (Scheme 2).

In summary, we have described a new protocol for regiospecific, anti-Markovnikov hydration of 3-arylpropargylic moiety under basic conditions. The protocol will likely be transferrable to other arylacetylenes. The generality of the newly identified method is currently under investigation in our laboratories. The results of an expanded study will be reported in due course.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.06.004.

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