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NH_4OAc Promoted Cyclocondensation of 3-(*o*-Allylphenyl)pentane-1,5-diones: Synthesis of Tetracyclic Benzofused 1-Azahomoisotwistanes

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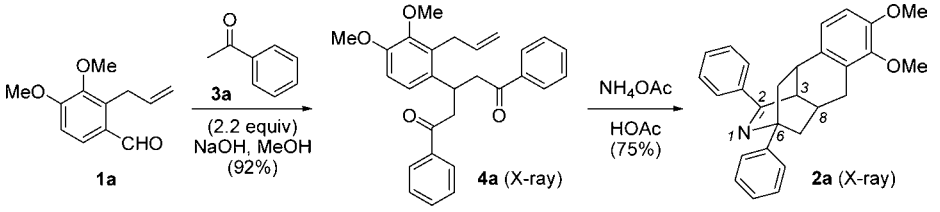
ABSTRACT



A facile two-step synthetic route for preparing the novel tetracyclic skeleton of benzofused 2,6-diaryl-1-azahomoisotwistanes 2 had been developed. The route was carried out by a one-pot tandem cross-coupling reaction of *o*-allylbenzaldehydes 1 with aryl methyl ketones 3, and NH_4OAc mediated the cascade cyclocondensation reaction of the resulting 1,5-diketones 4 with the 3-*o*-allylphenyl group in good yield in two steps.

For the preparation of the azaheterocyclic skeleton, ammonium acetate (NH_4OAc) has served as the nitrogen source in countless synthetic protocols and applications, for example, functionalized pyridines,[1] pyrroles,[2] homotropinones,[3] pyrimidines,[4] and imidazoles.[5] In particular, the pyridine ring system is of immense interest because of its synthetic approaches with diversified design, which are often characterized by the number of atoms in each fragment contributing to the six-membered skeleton, including (5 + 1), (4 + 2), (3 + 3), (3 + 2 + 1), or (2 + 2 + 2) routes.[6] Among the most synthetic approaches for the formation of the pyridine framework, NH_4OAc promoted the one-pot tandem condensation of arylaldehyde with 2 equiv of aryl methyl ketone which is a well established protocol under various conditions.[7]

In continuation of our recent investigation with the syntheses of some benzannulated molecules

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(e.g., tetrahydroanthracen-9-ones and isoquinolines),[8] a facile two-step synthetic route for preparing the novel tetracyclic skeleton of benzofused 2,6-diaryl-1-azahomoisotwistane was studied next. Natural products with the carbon structural framework of homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane), such as seychellene, patchouli alcohol and cannivonine, exhibited some interesting biological activities and were prepared by unique synthetic approaches as shown in Figure 1.[9]

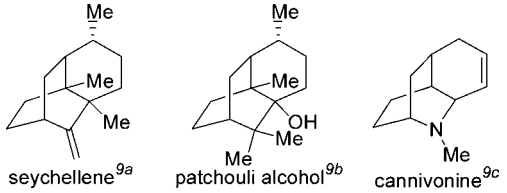
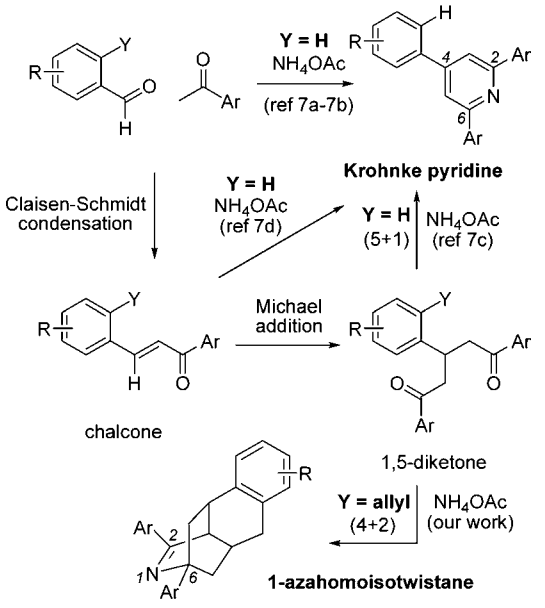


Figure 1. Natural products with the structural framework of homoisotwistane.

In the NH_4OAc mediated (5 + 1) cyclocondensation reaction, traditionally the Kröhnke pyridine with a 2,4,6-triaryl substitution pattern could be isolated under the solvent-free, catalyst-free, or microwave irradiation conditions via the intermediate of chalcone and 1,5-diketone (Y = H) as shown in Scheme 1.[10] With Y changed from hydrogen to the allyl group on the starting arylaldehyde (Y = allyl), the 1,5-diketone was isolated by a one-pot tandem cross-coupling reaction[11] (Claisen–Schmidt condensation/Michael addition) of *o*-allylbenzaldehyde with aryl methyl ketone in acceptable yields. Surprisingly, when treatment of 3-(*o*-allylphenyl)-1,5-diketone reacted with NH_4OAc, we observed that the novel tetracyclic benzofused skeleton of 1-azahomoisotwistane replaced the expected pyridine skeleton.[12] So far, there is still no example to describe the NH_4OAc promoted straightforward cyclocondensation reaction of 1,5-diketone with the 3-*o*-allylaryl substituent.

To initiate the synthetic work of skeleton **2**, 3-(*o*-allylphenyl)-1,5-diketone **4a** was first prepared via the one-pot tandem reaction of starting material **1a**[13] with **3a**

Scheme 1. Synthetic Routes of 2,4,6-Triarylpyridine (Y = H) and 2,6-Diaryl-1-azahomoisotwistane (Y = Allyl)



(R_1 = Ph) in a 92% yield under an alkaline aqueous–methanolic solution as shown in Scheme 2. Next, the tetracyclic benzofused 2,6-diphenyl-1-azahomoisotwistane **2a** was formed via a one-pot cascade cyclocondensation reaction of the resulting 1,5-diketone **4a** with NH_4OAc in 75% yield. By the above-mentioned synthetic procedure, changing different analogues **3b**–**3k**, 1,5-diketones **4b**–**4o** (66–92%) and 1-azahomoisotwistanes **2b**–**2o** (44–82%) were isolated, respectively. Therefore, in the case of **4n** and **4o** (R_1 = Me), only one diastereoisomer was eluted, corresponding to the steric effects; no other isomer was detected.[14]

Furthermore, **2a**, **2c**, **2j**, and **2n** were determined by single-crystal X-ray crystallography. Structure **2a** is shown in Figure 2. We also challenged the one-pot synthesis of **2a** via a NaOH-mediated reaction of **1a** and **3a**, followed by the addition of NH_4OAc in an alkaline solution. However, **2a** (48%) was only isolated by increasing the reaction time.

The formation of the tetracyclic adduct **2a** was confirmed through spectral analysis. The ^1H NMR spectrum of **2a** exhibited two doublets at δ 6.86 and 6.83 for benzofused protons. Three CH protons appeared as two doublets of H-3 (δ 3.48) and two multiplets of H-4 (δ 2.97) and H-8 (δ 2.25). Three CH_2 protons appeared as two triplets of H-5 (δ 1.93) and two doublets of doublets of H-7 (δ 1.81 and 1.73) and H-9 (δ 3.07 and 2.91). The structure of **2a** was confirmed by HRMS, which showed a peak at *m*/*z* 410.2125 [M^+ + 1].

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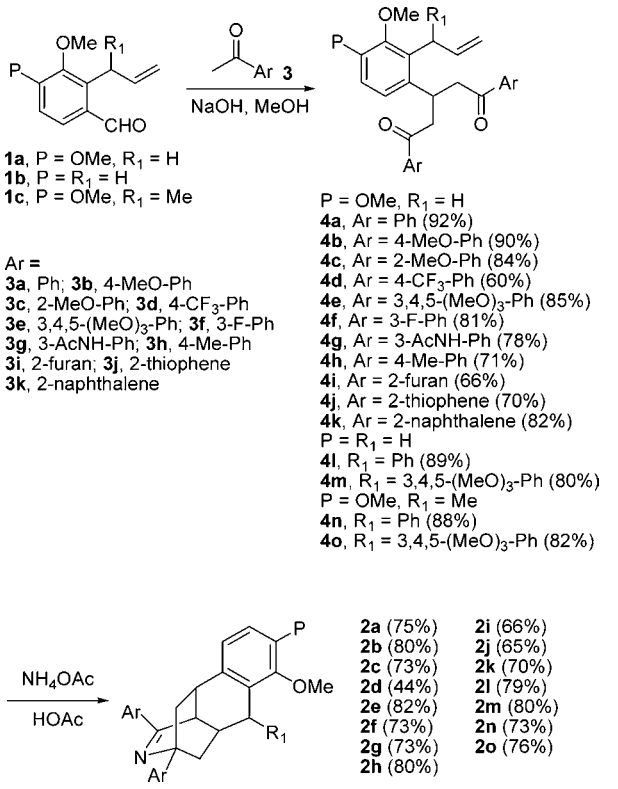
(13) The starting skeleton **1** was provided from commercially available isovanillin in moderate overall yields in three steps according to the reported procedures with the reaction sequence of O-allylation and Claisen rearrangement followed by O-methylation.

(14) CCDC 883599 (**2a**), 883600 (**2c**), 887548 (**2j**), 887547 (**2n**), 883594 (**4a**), and 883595 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44–1223–336033; E-mail: deposit@ccdc.cam.ac.uk).

Scheme 2. Synthesis of Skeleton **2**



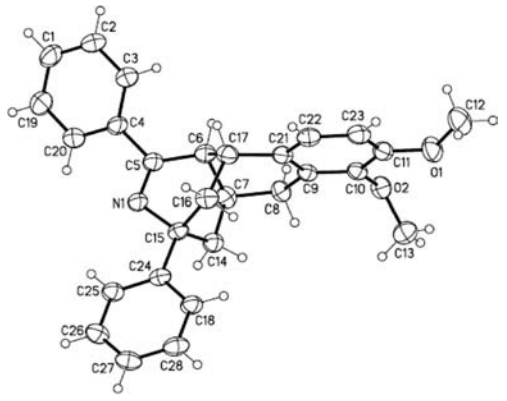
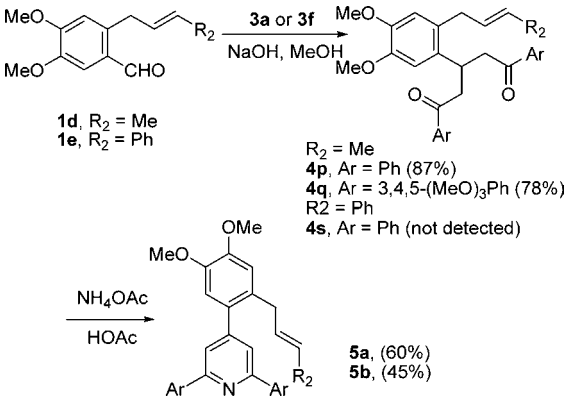


Figure 2. X-ray structure of **2a**.

To extend this protocol for the application of skeleton **4** with the 3-(2-butenylphenyl) group (**4p** or **4q** was prepared from the reaction of **1d** with **3a** or **3f** in 87% or 78% yield), we found that skeleton **5** was easily formed as a sole isomer (60% of **5a** or 45% of **5b**) under the NH_4OAc mediated one-pot conditions (Scheme 3). The possible explanation could be that the 2-butenyl side chain (R_2 = Me) of **4p** or **4q** inhibited the formation of skeleton **2** by the inherent steric hindrance. Therefore, the ring closure of **4p** or **4q** was then turned to form skeleton **5**. Other attempts to produce **4s** by treatment

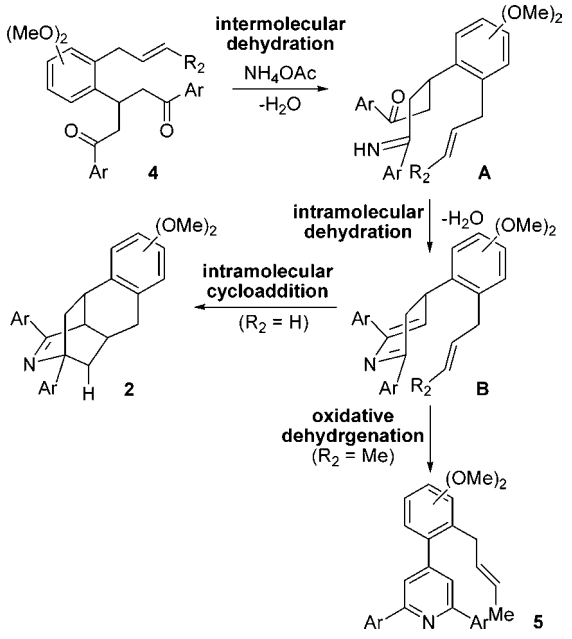
Scheme 3. Synthesis of 2,4,6-Triarylpyridines **5**



of **1e** (R_2 = Ph) with **3a** were unsuccessful due to the base-induced olefinic migration between the two aryl groups of **1e**.

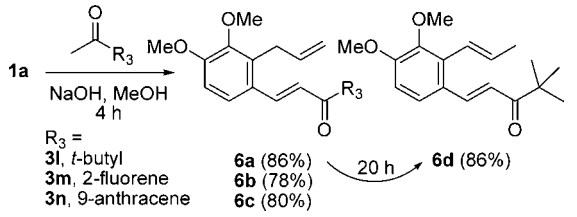
How are skeletons **2** and **5** produced? As shown in Scheme 4, the initial event may be considered as the formation of intermediate **A** with the imine skeleton by the NH_4OAc mediated intermolecular dehydration of the symmetrical 1,5-diketone **4**. Intermediate **B** is afforded from the intramolecular addition followed by dehydration. After the six-membered ring of intermediate **B** is generated, sequential intramolecular Diels–Alder cycloaddition of intermediate **B** with the dehydropyridine skeleton affords **2** (R_2 = H). When R_2 is the methyl group, pyridine skeleton **5** is immediately formed via oxidative dehydrogenation due to the repulsion hindrance between the diene and dienophile with the R_2 group of intermediate **B**. The results suggested that the steric conformation derived from the

Scheme 4. Possible Mechanism for the NH_4OAc Mediated Annulation

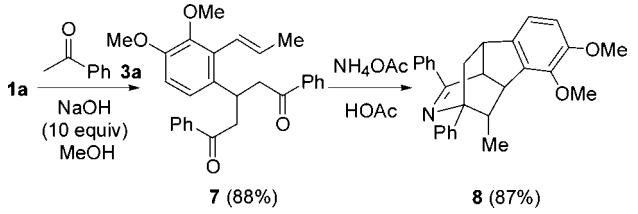


R_2 group might have caused the preference of pyridine formation rather than [4 + 2] cycloaddition. Therefore, the bridged skeleton **2** with three six-membered rings and the symmetrical pyridine skeleton **5** with 2,4,6-triaryl groups

Scheme 5. Reaction of **1a** with **3l**–**3n**



Scheme 6. Synthesis of **8**



are efficiently constructed, respectively, by the one-pot cascade cyclocondensation reaction.

Under similar conditions, reactions of **1a** with **3l**–**3n** were further studied, as shown in Scheme 5. By controlling the bulky size of the R_3 group (*tert*-butyl, 2-fluorenyl, or 9-anthracenyl), only the aldol skeleton **6** was isolated. By increasing the reaction time (20 h), solely **6d** with the (*E*)-form olefin was obtained in 86% yield by the olefin migration under alkaline conditions. From the observation, we envisioned that the bulky group (R_3 group) should be the key factor affecting the Michael addition of the second methylketone.

Using the facile route, the efficient transformation from **1a** to **8** could be performed in high yield and in two steps. First, compound **7** was prepared in 88% yield from the reaction of **1a** with excess NaOH (10.0 equiv) by the one-pot combination of Claisen–Schmidt condensation/Michael addition/olefin migration. Then, 1-azaisotwistane **8** was isolated in 87% yield by NH_4OAc mediated cyclocondensation (Scheme 6). Furthermore, the structural framework of **8** was determined by single-crystal X-ray crystallography. X-ray diffraction analysis could be employed to prove the constitution and relative configuration.[14]

In summary, we have successfully presented a synthetic methodology for the skeleton of tetracyclic 1-azahomoisotwistane **2**, which involved one-pot tandem cross-coupling of *o*-allylbenzaldehyde **1** with aryl methyl ketone **3**; NH_4OAc promoted the cascade cyclocondensation of the resulting 1,5-diketone **4** with the 3-*o*-allylphenyl group in good yield in two steps. The novel strategy showed that NH_4OAc is an excellent nitrogen source with which to promote the formation of the tricyclo[5.3.1.$0^{3,8}$]undecane structure. Considering the utility of these polycyclic benzofused compounds, the development of these general synthetic approaches is significant.

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Supporting Information Available. Experimental procedures, characterization data, scanned photocopies of ^1H and ^{13}C NMR of new compounds, and crystallographic data of compounds **2a**, **2c**, **2j**, **2n**, **4a**, and **8** (CIF) were supported. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.