THREE-COMPONENT SYNTHESIS OF INDOLIZINES FROM AZAAROMATIC-ACETYLENEDICARBOXYLATE ZWITTERIONS WITH ACYLZIRCONOCENE CHLORIDE COMPLEXES

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Abstract – Acylzirconocene chloride complexes worked well as a reaction partner of azaaromatic-acetylenedicarboxylate zwitterions derived from isoquinolines or pyridines with diethyl acetylenedicarboxylate to afford the corresponding indolizine derivatives.

The diverse reactivity of azaaromatic-acetylenedicarboxylate zwitterions, which are easily generated by the addition of azaaromatic compounds such as pyridines and isoquinolines to acetylenedicarboxylates, provides a useful tool for the construction of the highly functionalized and/or polycyclic N-heterocycles. In the pioneering work, Huisgen showed that the trapping of the azaaromatic-acetylenedicarboxylate zwitterions with external dipolarophiles (phenyl isocyanate, diethyl mesoxalate and dimethyl azodicarboxylate) led to the corresponding six-membered ring-fused heterocycles. In recent years, such a strategy for the six-membered ring formation using the azaaromatic-acetylenedicarboxylate zwitterions with various imines, ketones or electron-deficient olefins has been thoroughly investigated by Nair’s and some research groups (Scheme 1, route a). Furthermore, 1,4-addition of enolates, terminal alkynes or hetero nucleophiles to the azaaromatic-acetylenedicarboxylate zwitterions has been disclosed (route b). Although the azaaromatic-acetylenedicarboxylate zwitterions can be employed for the synthesis of indolizine derivatives, which constitute the core structure of many naturally occurring alkaloids and biologically active compounds, most of these reaction partners are ketones possessing a leaving group at the α-position (route c). We described herein the three-component synthesis of indolizine derivatives using acylzirconocene chloride complexes as a novel partner of azaaromatic-acetylenedicarboxylate zwitterions (route d).
Our continuous study about the reactivity of easily accessible and stable acylzirconocene chloride complexes, which are prepared by the hydrozirconation of unsaturated compounds and the subsequent insertion of carbon monoxide, has indicated that the acylzirconocene chlorides work as a donor of ‘unmasked’ acyl anion in organic syntheses. Recently, we developed the direct introduction of acyl groups into azaaromatic compounds using acylzirconocene chlorides through the Reissert-type acylation of azaaromatics activated by chloroformates. Therefore, as in the Reissert-type acylation reaction, acylzirconocene chloride would be expected to bring about the nucleophilic addition to the activated C=N bond of azaaromatic-acetylenedicarboxylate zwitterions, thereby leading to the indolizine products via the cyclocondensation of acyl adduct intermediates (Scheme 1, route d). At the outset, the reaction of isoquinoline (2a) and diethyl acetylenedicarboxylate (DEAD, 1 equiv) with 1 (2 equiv) in CH$_2$Cl$_2$ was examined. It turned out that the desired indolizine 3a was obtained in 77% yield at ambient temperature for 3 h without any catalyst (Scheme 2). The structure of 3a was determined by various spectra of 3a, and by comparison with the reduced product of indolizine 5, which was prepared from 2a, DEAD and $\alpha$-nitroketone 4 according to Yavari’s procedure (Scheme 3). As well as 2a, the substituted

**Scheme 1.** Trapping of azaaromatic-acetylenedicarboxylate zwitterions with various partners

**Scheme 2.** Three-component synthesis of indolizines 3 from isoquinolines 2 and DEAD with 1
Scheme 3. Two-step synthesis of indolizine 3a from 2a and DEAD with α-nitroketone 4

Isoquinolines 2b-d in the presence of DEAD readily reacted with 1 to give the corresponding indolizines 3b-d in 48-92% yields (Scheme 2).

As shown in Scheme 4, the present procedure was successfully extended to the reaction of pyridines 6. Thus, under the similar conditions to isoquinolines 2, pyridine (6a) and 3,5-dimethylpyridine (6b) afforded indolizines 7a and 7b in 67% and 54% yields, respectively. In the case of 3-substituted pyridine 6c, which brought about indolizines 7c and 8c as a regioisomeric mixture (7c: 51%, 8c: 24%) at 50 ºC, 7c was preferentially formed via the addition of acyl group to the 2-position of the 6c-DEAD zwitterion. The 2-acylation of the zwitterion may be due to an interaction between 1 and 3-CO₂Me group of the zwitterions. The similar discussion was suggested in the Reissert-type reaction of 3-substituted N-(alkoxycarbonyl)pyridinium salts with organostannanes.¹⁶

Scheme 4. Three-component synthesis of indolidines 7 and/or 8 from pyridines 6 and DEAD with 1

In conclusion, we have demonstrated the three-component synthesis of indolizines from isoquinolines or pyridines, diethyl acetylenedicarboxylate and acylzirconocene chloride complex. These findings indicate a new possibility for the use of acylzirconocene chloride complexes in organic synthesis. Synthetic applications and detailed mechanistic studies of the present reaction are underway.
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REFERENCES AND NOTES


