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CONDENSATION REACTIONS OF α-AMINO-ZINCENAMINES WITH ALDEHYDES; APPLICATION TO INDOLIZINES

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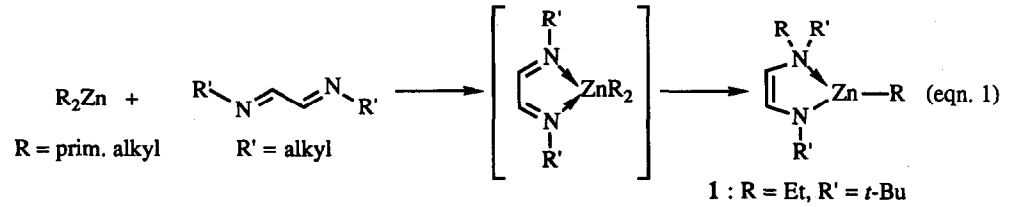
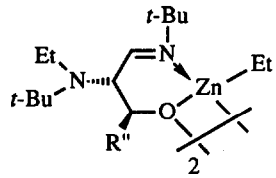
*Abstract: The zinc-enamine **1** is easily accessible via the reaction of Et_2Zn with t-BuN=CHCH=Nt-Bu and is reactive towards aldehydes. The condensation reaction of **1** with 2-pyridine-carboxaldehyde results in the thermally instable zinc-aldolate **2b** that subsequently rearranges to the indolizine **4**.*

Since their discovery by Wittig[1] the metalloenamines were recognized as successful alternatives for the metalloenolates in several C-C coupling reactions.[2] Metalloenamines are commonly prepared by regioselective deprotonation of an imine by a non-nucleophilic base. Recently, we developed a novel route for the synthesis of metalloenamines starting from α-diimines (R'N=CHCH=NR', R'DAB) and diorganozinc compounds, see eqn.1.[3] This route involves the formation of a 1 : 1 coordination complex, that undergoes a quantitative and regioselective alkyl group transfer from zinc to a nitrogen-atom of the chelating DAB system. The resulting organozinc-enamines (e.g. **1**: R = Et, R' = *t*-Bu) show interesting reactivities towards electrophiles, like aldehydes, and some examples are given here.



Zinc-enamine **1** reacts in diethyl ether quantitatively with aldehydes (equimolar amounts) at 0 °C to zinc-aldolate products with a moderate to excellent diastereoselectivity (40->99%). Although **1** has a *Z*-configuration, as a result of intramolecular Zn-N coordination (*cf.*, ref.3), which would give rise to formation of *syn* aldols,[8] the main aldol products have an *anti* configuration due to the steric demand of the *t*-Bu(Et)N group. Reactions of **1** with an aldehyde (R"CHO), that has a relatively small R"-group (e.g., propionaldehyde) result in the formation of a zinc-aldolate with a *syn* : *anti* ratio of 40 : 60, whereas for benzaldehyde with the larger phenyl group this ratio increases to 1 : 99. The presence of the newly formed C-C bond in the zinc-aldolates was indicated by a characteristic ABX pattern for the H^a, H^b and H^x protons in the *t*-BuN=CH^a-CH^b(N*t*-Bu(Et))-CH^xR"-O monoanionic moiety.[7] The zinc-aldolates exist in benzene as dimeric species (determined by cryoscopic molecular weight measurements) containing intramolecular six-membered chelate rings, as shown in eqn. 2.[8] Such dimeric units are also present in the crystal structure of the 1 : 1 complex of **2c** with $ZnEt_2$. There, two pyridine nitrogens of different **2c** dimeric units complex to a bridging $ZnEt_2$ molecule, resulting in the formation of a unique coordination polymer.[9]

The organic aldolates were isolated as TMS protected aldolates, *t*-BuN=CH-CH(N*t*-Bu(Et))-CHR"-OTMS, by quenching of the zinc-aldolates with 1 equivalent of TMSCl (see scheme 1, route 2).

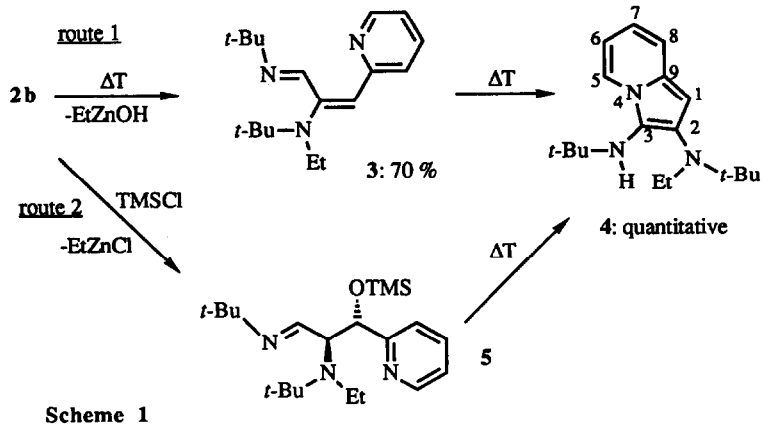


1 $\xrightarrow[Et_2O]{R"CHO}$ **2**

2a: R" = Ph, >99 % anti
2b: R" = 2-pyridine, >99% anti
2c: R" = 4-pyridine, >99% anti
2d: R" = Et, syn : anti = 30 : 70
2e: R" = *i*-Pr, syn : anti = 15 : 85

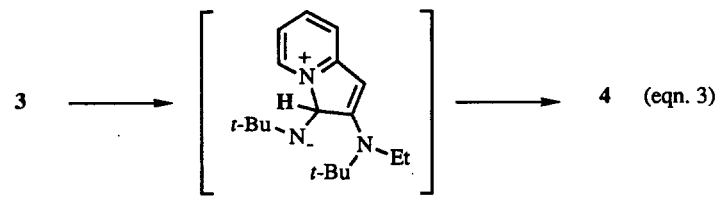
(eqn. 2)

Interesting further reactivity was found when we studied the influence of coordinating atoms in the aldehydes used. This resulted in the finding of a simple route for the synthesis of 2,3-diaminoindolizines (**4**) *via* the condensation reaction of the organozinc-enamine **1** with 2-pyridine-carboxaldehyde, see scheme 1. Upon subsequent heating of **2b** in benzene at 50 °C for 1 hour, elimination of EtZnOH occurs, leading to a compound of which the ^1H and ^{13}C NMR spectra are in accordance with the unsaturated species **3** (see scheme 1).[10] Complex **3** converts completely to the isomeric indolizine **4** upon further heating at 80 °C in benzene for 76 hour and was isolated in 70 % yield, based on the amount of starting compound **2b**. The ^1H NMR spectrum of **4** shows a broad N*H* signal (H/D exchange was observed upon addition of EtOD) at 2.90 ppm and 5 aromatic protons with a characteristic singlet for the proton at position 1, see scheme 1. Alternatively, **4** could be obtained in an even higher yield *via* the TMS-aldolate **5**, see scheme 1, by heating of **5** in benzene at 80 °C for four hours. In this reaction sequence the intermediacy of **3** was not observed.



Scheme 1

The formation of **4** probably involves the elimination of EtZnOH or TMSOH from the *anti* zinc-aldolate **2b** in an E_2 reaction, leading to the *E* configuration of **3**. A subsequent intramolecular nucleophilic attack of the pyridine lone-pair at the imine carbon then gives **4** *via* the zwitter-ionic intermediate **3a**. The latter subsequently rearranges *via* a 1,2 H-shift from the formal imine carbon to the nitrogen atom. The present Lewis acids, zinc salts in route 1 and $(TMS)_2O$ in route 2 (see scheme 1), may favour the formation of **3a** by stabilizing the negative charge on the nitrogen atom. The effect of Lewis acids on this cyclization reaction to the indolizine was shown by a 40-fold increase in the rearrangement rate of pure **3** to **4** upon addition of TMSOH.[11] Overall, the driving force for the rearrangement of **3** to the indolizine **4** is the formation of an aromatic species with a delocalized 10π-electron system.



3a

Several synthetic routes for indolizines are known[5] of which the one starting from 2-(2-cyanovinyl)-pyridines to give 3-aminoindolizine[6] is related to that presented here. It was suggested that the final ring closure step from the 2-(2-cyanovinyl)pyridine to the 3-aminoindolizine proceeds *via* a reduction of the nitrile to an imine function. In our route we were able to isolate and characterize the imine intermediate (**3**), which upon heating gave **4** quantitatively. Further work is in progress directed to reactions with R'DAB substrates that have R' groups that are easily removable from the resulting indolizine products.

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References and Notes

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6. Flitsch, W.; Kahner-Gröne, S. *Chem. Ber.* **1982**, *115*, 871.
7. All zinc-aldolates have been fully characterized by 300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR.
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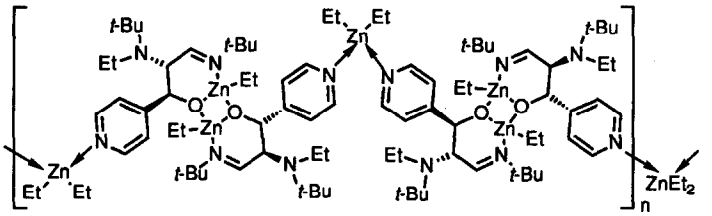
9. Crystal-structure of the coordination polymer of **2c** (see figure below) is to be published.



10. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 MHz spectrometer in C_6D_6 at room temperature. ^{1}H NMR of **3**: δ 8.92 (d, 1H, pyridine), 8.58 (d, 1H, pyridine), 7.80 (s, 1H, N=C*H*), 7.42 (s, 1H, C=C*H*), 7.19 (dt, 1H, pyridine), 6.63 (dt, 1H, pyridine), 3.31 (q, 2H, NC*H*$_2$CH$_3$), 1.27 (s, 9H, C(C*H*$_3$)$_3$), 1.15 (t, 3H, NCH$_2$C*H*$_3$), 1.11 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR of **3**: δ 157.4 N=*C*, 156.9, 149.8 pyridine, 147.8 *C*=CH, 140.8 C=*C*H, 134.8, 124.7, 122.0 pyridine, 57.2, 55.9 *C*(CH$_3$)$_3$, 39.8 NCH$_2$CH$_3$, 29.5, 29.0 C(CH$_3$)$_3$, 15.7 NCH$_2$CH$_3$. ^{1}H NMR of **4**: δ 8.19 (d, 1H, pyridine), 7.12 (d, 1H, pyridine), 6.43 (dt, 1H, pyridine), 6.29 (s, 1H, C=C*H*-C$_5$H$_4$N), 6.24 (dt, 1H, pyridine), 3.03 (q, 2H, NC*H*$_2$CH$_3$), 2.90 (bs, 1H, N*H*), 1.21, 1.06 (s, 9H, C(C*H*$_3$)$_3$), 1.00 (t, 3H, NCH$_2$C*H*$_3$). ^{13}C NMR of **4***: δ 132.1 C(3), 127.7 C(2), 125.3 C(9), 122.5 C(5), 118.5 C(8), 115.7 C(7), 108.7 C(6), 95.7 C(1), 57.0, 55.0 *C*(CH$_3$)$_3$, 44.1 NCH$_2$CH$_3$, 31.2, 27.8 C(CH$_3$)$_3$, 15.7 NCH$_2$CH$_3$. Anal. Calcd of **4**, for C$_{18}$H$_{29}$N$_3$: C, 75.21; H, 10.17; N, 14.62. Found: C, 75.17; H, 10.20; N, 14.69. *The numbering of the carbon atoms are in accordance with the generally accepted numbering system of indolizines (see scheme 1).
11. TMSOH was separately prepared by hydrolyzation of TMSCl with 1 equivalent of H_2O in diethyl ether. The mixture was carefully distilled prior to use. It is of common knowledge that TMSOH rearranges to H_2O and TMSOTMS and it is therefore noteworthy to mention that upon addition of TMSOTMS no rearrangement from **3** to **4** takes place, whereas upon addition of 1 molar equivalent of H_2O to the mixture of **3** and TMSOTMS the reaction proceeds.

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