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Addition Reactions and Redox Esterifications of Carbonyl Compounds by *N*-Heterocyclic Carbenes of Indazole

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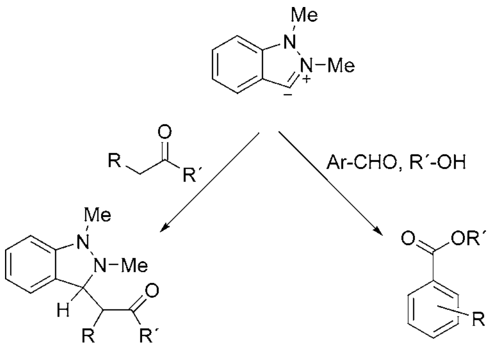
ABSTRACT



Thermal decarboxylation converts 1,2-dimethylindazolium-3-carboxylate into indazol-3-ylidene, which reacts in situ with ketones to form stable 1:1 adducts. When the reaction is conducted with aromatic aldehydes in alcohols, redox esterifications to benzoates are observed. Model reactions such as redox esterifications of aromatic aldehydes with sodium alcoholates in the presence of 1,2-dimethylindazolium salt and oxidations of sodium benzylates by 1,2-dimethylindazolium salt to aldehydes lend support to a Cannizzaro-type mechanism of this reaction.

N-Heterocyclic carbenes (NHC) have attracted considerable attention in the past few years from both a synthetic and a theoretical point of view. In the chemistry of carbonyl compounds, they have been utilized not only as organocatalysts for the benzoin condensation,[1] Stetter reaction,[2] and transesterifications[3] but also for C−C bond cleavages in redox esterifications of chiral formylcyclopropanes[4] and syntheses of (*E*)-β-unsaturated esters starting from alkynyl aldehydes,[5] saturated esters from α,β-unsaturated aldehydes,[6] or α-haloaldehydes[7] and of β-hydroxy esters from epoxyaldehydes.[8] A literature survey on heterazolium-catalyzed

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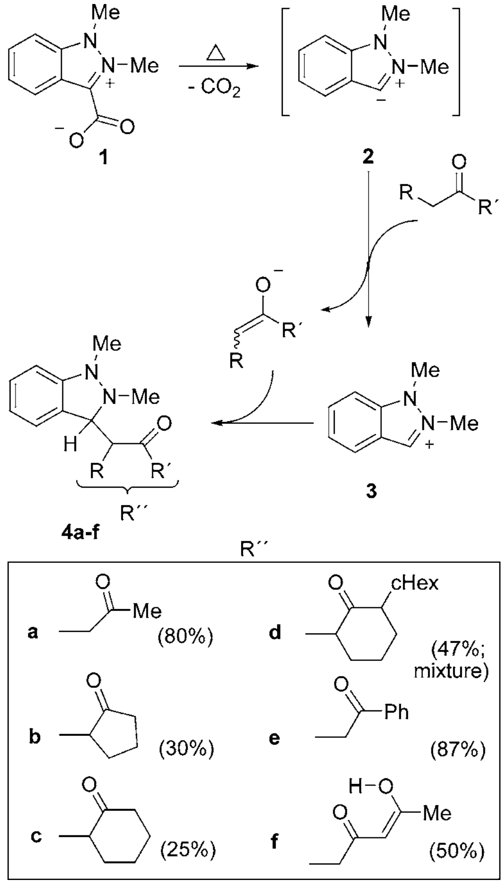
reactions appeared recently.[9] Moreover, interesting stoichiometric reactions between NHCs and various substrates have been reported.[10] In the majority of these reactions, NHCs are generated by deprotonation of cationic precursors. Alternative approaches for the generation of *N*-heterocyclic carbenes are thermal eliminations, either starting from 2-alkoxy-substituted imidazolidines or 2,3-dihydro-1*H*-imidazoles[11] or from pseudo-cross-conjugated heterocyclic mesomeric betaines (PCCMB). Thus, pyrazolium-3-carboxylates,[12] indazolium-3-carboxylates,[13,14] imidazolium-2-carboxylates,[15] pyridinium-2-carboxylates,[16] and quinolinium-2-carboxylates[17] undergo thermal decarboxylations to *N*-heterocyclic carbenes, whereas indazolium-3-amidates extrude isocyanates to NHCs.[13] We report here unexpected reactions between the NHC of indazole and aldehydes as well as ketones.

In situ generation of the *N*-heterocyclic carbene **2** by thermal decarboxylation of 1,2-dimethylindazolium-3-carboxylate **1**[14] in acetone resulted in the formation of the stable 1:1 adduct **4a** in 80% yield (Scheme 1). We assume that the carbene deprotonates the acetone (pK_a 26.5)[18] and that the resulting enolate adds to the iminium bond of the indazolium cation **3**. This is in accord with the observation that indazolium salts can be silylated with *t*-BuPh$_2$SiLi or methylated with methyllithium at C-3.[19]

Scheme 1. Reaction of NHC **2** with Ketones



This reaction was also applied to cyclic ketones such as cyclopentanone (pK_a 25.8), cyclohexanone (pK_a 26.4), and 2-cyclohexylcyclohexanone, which gave the adducts **4b**−**d**, respectively.[20] Under the reaction conditions applied, the latter mentioned ketone formed a 1:1 mixture of isomers, resulting from deprotonation of either α-hydrogen atom. Acetophenone (pK_a 24.7) gave **4e** in 87% yield. Acetylacetone (pK_a 13.3) reacted via the terminal methyl group to give the adduct **4f**, 83% of which exists in its enol form in CDCl$_3$ solution at rt. To the best of our knowledge, no analogous reaction have been observed with known *N*-heterocyclic carbenes. *N*-Alkoxycarbonyl-substituted imidazolium, thiazolium, and benzothiazolium salts, however, are able to add in situ generated silyl enol ethers to 2-substituted imidazolines and thiazolines.[21] On performing similar reactions with aromatic aldehydes in alcohols, oxidative esterifications were observed. Thus, heating a mixture of mesomeric betaine **1** and the aldehydes **5a**−**f** in ethanol, *n*-propanol, and *n*-butanol, respectively, resulted in the formation of benzoates **6a**−**i** (Scheme 2).[22] Unreacted aldehydes were recovered.

In order to gain information about the mechanism of this redox esterification, we carefully analyzed the reaction mixtures and performed ab initio calculations[23] as well as model reactions. Tetrahedral intermediates such as **I** (Scheme 3) are formulated in essentially all *N*-heterocyclic carbene catalyzed transformations of aldehydes, and a common premise in the additions of umpolung species to aldehydes

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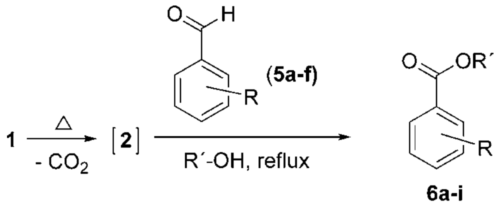
(20) Typical procedure: The mesomeric betaine **1** (95 mg, 0.5 mmol) was suspended in 4.5 mL of the ketone and heated at 60−75 °C for 1−2 h. The reaction was monitored by TLC. The excess ketone was distilled off under reduced pressure, and the residue was chromatographed (silica gel, petroleum ether/ethyl acetate = 4 / 1). Thus, 2-(1,2-dimethyl-2,3-dihydro-1*H*-indazol-3-yl)cyclopentanone **5b** was obtained as a yellow oil, yield 30 mg (30 %).

(21) Itoh, T.; Miyazaki, M.; Nagata, K.; Ohsawa, A. *Tetrahedron* **2000**, *56*, 4383.

(22) Typical procedure: The mesomeric betaine **1** (0.25 mmol, 48 mg) and benzaldehyde (0.25 mmol) were dissolved in 10 mL of alcohol. The mixture was then heated over a period of 3 h. After evaporation of the solvent, the mixture was chromatographed on silica gel with petroleum ether/ethyl acetate (30:1) to separate ethyl benzoate **6a (**13 mg) from unconsumed benzaldehyde (34 mg).

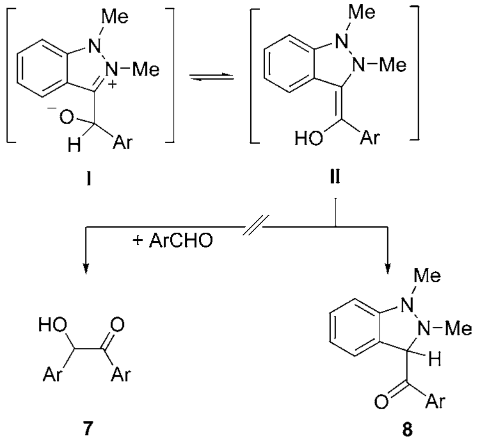
Scheme 2. Redox Esterifications of Aldehydes



6	R	R′	yield
a	H	Et	49%
b	4-Et	Et	51%
c	4-OMe	Et	69%
d	2,4-Cl$_2$	Et	22%
e	2-Me	Et	33%
f	4-NMe$_2$	Et	80%
g	4-NMe$_2$	nPr	93%
h	4-NMe$_2$	nBu	47%
i	4-NMe$_2$	iPr	49%

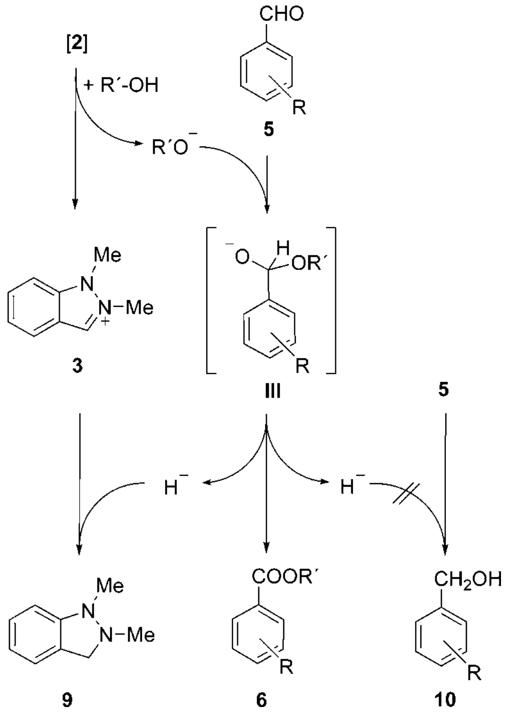
(benzoin reaction) and conjugate acceptors (Stetter reaction) is its conversion to a “Breslow intermediate” **II**.[24] However, in the reaction described here, no traces of benzoins **7** were found. On performing the reaction with 2-methylbenzaldehyde, however, we were able to isolate the 3-acyl-2,3-dihydro-1*H*-indazole **8** as a representative of a rather rarely described class of compounds. Indazole **8** is a tautomer of **II** and was isolated in 22% yield. This finding proves the nucleophilic properties of NHC **2** toward aldehydes.

Scheme 3. Breslow Intermediates and Tautomers



Taking the basicity of carbene **2** into consideration, a Cannizzaro-type reaction mechanism can be proposed under the reaction conditions applied (Scheme 4).

Scheme 4. Proposed Mechanism



We propose that the in situ generated NHC **2** deprotonates the alcohols to form indazolium salt **3** and alcoholates which is an endothermic process (+9.3 kcal/mol) according to the ab initio calculations.[25] The alcoholate then attacks the carbonyl group of the benzaldehydes to intermediates **III** (−3.0 kcal/mol). Hydride transfer to a second molecule of aldehyde was excluded from consideration in view of results of model reactions (vide infra) and the fact that we never detected benzylic alcohols in our reaction mixtures. Although this step was calculated to be exothermic (−8.4 kcal/mol), the disproportionation of the indazolium salt **3** and intermediate **III** to 2,3-dihydro-1*H*-indazole **9** and the ester **6** is indeed energetically strongly favored (−34.7 kcal/mol).

To prove this mechanistic proposal, we reacted indazolium salt **3** successfully with benzaldehydes in the presence of stoichiometric amounts of sodium ethanolate to the benzoic acid esters **6b**,**c**,**e** (Scheme 5). This is a model reaction for the oxidation of Cannizzaro-intermediate **III**.

The indazolium salt **3** is also able to oxidize freshly prepared sodium benzylates under inert and anhydrous atmospheres to benzaldehydes, forming **9** which was detected by GCMS (Scheme 6). As examples, the reaction was applied to sodium 2,4-dichlorobenzylate, 4-ethylbenzylate, and 2-methylbenzylate, respectively, which gave the corresponding aldehydes **5b**,**c**,**e** in up to 75% isolated yield (Scheme 5). Benzylic alcohols, if formed at all in Cannizzaro-type processes, obviously oxidize to aldehydes under these reaction conditions. Indeed, the calculation predicted that protonation of benzylate by the solvent EtOH is disfavored

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(23) Reaction energies for all pathways in consideration have been calculated at DFT level of theory using the B3LYP functional and the 6-311+G(d, p) basis set. All calculations include zero-point vibrational energy and account for solvent effects by the self-consistent reaction field method, utilizing the polarizable continuum model with a dielectric constant of $e_{\mathrm{r}} = 24.55$ for the solvent ethanol. All calculations have been performed with the program Gaussian 03.

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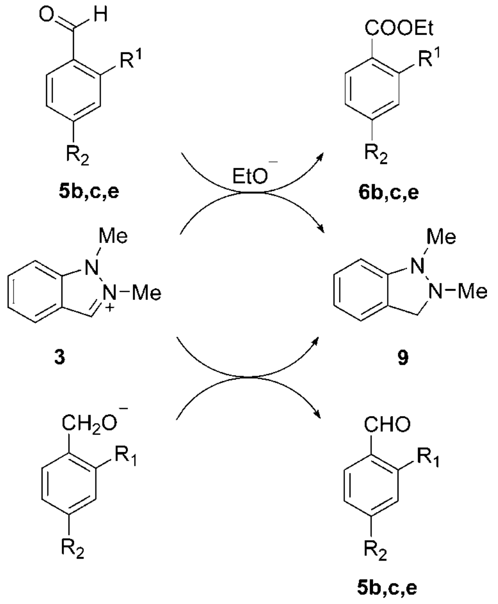
(25) All calculations were performed for benzaldehyde and ethanol.

Scheme 5. Model Reactions

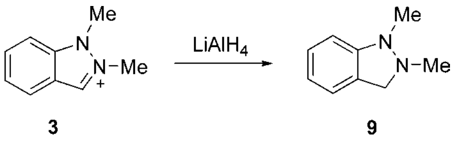


	R^1	R^2	yield
5b	H	Et	71%
5c	H	OMe	54%
5e	Me	H	75%
6b	H	Et	17%
6c	H	OMe	66%
6e	Me	H	26%

(+2.4 kcal/mol) in comparison to the redox reaction of indazolium salt **3** to **9** and benzylate to benzaldehyde (−26.3 kcal/mol).

In another model reaction, the indazolium salt **3** was reduced by $LiAlH_4$ in ether to give **9** in 85% yield as a yellowish liquid. In accordance with our findings, the resulting 2,3-dihydro-1,2-dimethyl-1*H*-indazole **9** decomposes on treatment with bases as well as in the presence of alcohols and silica gel on warming under reconstitution of indazolium salt **3**. Indeed, this salt could easily be separated from all reaction mixtures of the series of reactions described here by simple silica gel filtration.

Scheme 6



In summary, we can conclude that the pseudo-cross-conjugated heterocyclic mesomeric betaine 1,2-dimethylindazolium-3-carboxylate **1** decarboxylates thermally in the presence of carbonyl compounds to an *N*-heterocyclic carbene **2** which obviously acts as a strong base. Its protonation gives the corresponding indazolium salt **3**, which plays either a crucial role as electrophilic iminium salt toward enolates, or as oxidizing agent in redox esterifications of aromatic aldehydes in alcohols as well as of benzylates to aldehydes. Thus, the reactions described here differ from reactions of other *N*-heterocyclic carbenes.

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Supporting Information Available: Experimental procedures, full spectroscopic data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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