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C–H amination of enolizable and nonenolizable ketones†

Oksana Holovko-Kamoshenkova,[a,c] Zdeněk Tošner,[a] Ivana Císařová[b] and Radim Hrdina *[a]

We present a method for the amination of enolizable and non-enolizable ketones in the alpha (or beta) position to the carbonyl group. This approach is based on the conversion of the corresponding cyanohydrins to carbonazidates, precursors for thermal intramolecular nitrene insertion reactions into the adjacent C–H bond. Hydrolysis of the resulting carbamates under basic conditions with simultaneous regeneration of the carbonyl group yields amino ketones.

α-Amino ketones are common motifs in medicinal chemistry and drug design of antidepressants, appetite suppressants, and ACE-inhibitors and are versatile reagents in organic chemistry for the preparation of heterocycles and other synthetic building blocks.[1] There are several methods for producing this type of structural pattern. α-Amino ketones, derived from enolizable precursors, are typically prepared by α-deprotonation of the starting material and a subsequent reaction with an electrophile.[2–8] This electrophile is either a nitrogen-containing moiety or a group which is then subjected to a substitution reaction with nitrogen-based nucleophiles. Carbonyl α-aminations are performed also under reverse polarity mode using nitrogen nucleophiles.[9] α-Amino ketones can be prepared by means other than functionalisation of the C–H bond adjacent to the carbonyl group, such as transformation of α-amino acids, aza-benzoin condensation reactions, transfer hydrogenation of alpha hydroxy imines, hydrolysis of substituted triazoles, ring opening of azetidine-3-ols, one pot oxidation of unsaturated carbon–carbon bonds, reductive coupling reactions between imines and nitriles, oxidation of enamines, functionalization of enones and other synthetic approaches.[10] A further synthetic option to generate α-nitrogen substituted compounds is the conversion of a carbonyl to a transient directing group, which is then used for C–H functionalisation reactions.[11] Preparation of β-amino ketones[12] may rely on C–H activation strategies as well.[13] To the best of our knowledge, the conversion of ketones to cyanohydrins and the use of such a moiety for intramolecular C–H amination reactions[14] *via* nitrene insertions[15–17] has not been explored. Intramolecular C–H amination reactions for the preparation of carbamates from monosubstituted alcohol derivatives as starting materials are well known and can be divided into two main categories; transition metal nitrenoid insertion reactions into C–H bonds[18] and metal-free generation of reactive nitrene intermediates[19] (under thermal or photochemical conditions)[20] that insert into C–H bonds. There are various precursors for generation of alkoxycarbonylnitrene intermediates such as carbamates ($ROCONH_2$)[21–24] and their oxidation, carbonazidates ($ROCON_3$)[25–27] and their molecular nitrogen extrusion or *N*-oxidised carbamates (ROCONHOR′)[28,29] and their R′OH elimination (Fig. 1).

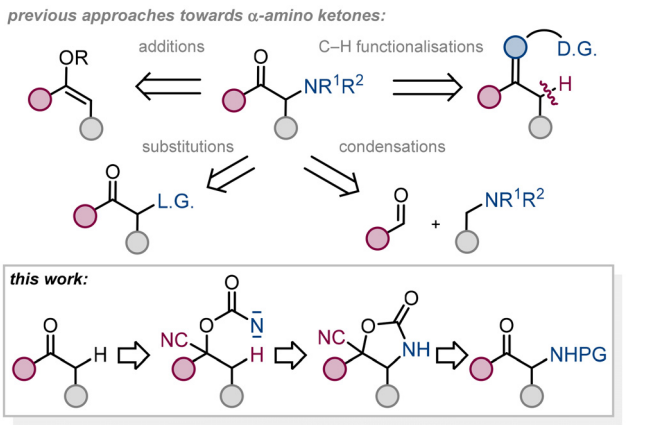

Fig. 1 C–H insertion reaction of nitrenes derived from cyanohydrin carbonazidates.

[a]*Charles University, Faculty of Science, Department of Organic Chemistry, Hlavova 8, 12840 Praha, Czech Republic. E-mail: hrdina@natur.cuni.cz*
[b]*Charles University, Faculty of Science, Department of Inorganic Chemistry, Hlavova 8, 12840 Praha, Czech Republic*
[c]*Uzhhorod National University, Narodna ploshcha 3, 88000 Uzhhorod, Ukraine*

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As a precursor for the generation of reactive nitrene intermediates, we decided to convert the hydroxy group of cyanohydrins to a versatile carbonazidate and use this moiety for molecular nitrogen extrusion reactions, which can theoretically be carried out under thermal or photochemical conditions or metal promotion, and a subsequent intramolecular insertion reaction of the generated nitrene species into the C–H bond, taking into account the influence of the incorporated cyano group on the reaction progress under different conditions. Eight different ketones **1** were converted to cyanohydrins **2** using various methods including the recent protocol of Zheng and Zhou.[30] The prepared cyanohydrins do not require further purification and can be used directly in the next step, formation of carbonazidates (Fig. 2).

To avoid multiple manipulations with hazardous chemicals such as triphosgene or sodium azide, we have used a procedure[31] to prepare the corresponding carbonazidates in one pot (Fig. 3). Pyridine was chosen as the solvent, and all compounds, sodium azide, starting material **1** and triphosgene, were added subsequently at −20 °C and the reaction mixture was stirred first at 24 °C for 1 hour and at 50 °C for a further 5 hours. The inorganic compounds were extracted into water and the desired product **3** was extracted into ethyl acetate. All carbonazidates **3** prepared in this way are bench stable, can be concentrated under vacuum and were isolated in yields ranging from 67% to 84%.

The diamantane[32,33] derivative **3h** was chosen as a model compound for the desired amination reaction (Fig. 4). All compounds **3** are well soluble in 1,2-dichloroethane, which is often the solvent of choice for such C–H amination reactions. The conditions for thermal reactions were first investigated. Two compounds of **4h** were prepared and isolated in good yields. The structure of **4h2** was confirmed by X-ray crystallography. Dilution (0.7 mmol of the corresponding carbonazidate in 5 mL of dry DCE) and 130 °C were then used for all substrates **3**.

The reaction with **3h** was then carried out under UV irradiation (254 nm) at 24 °C in CH_2Cl_2. The conversion was complete, and the ratio of isomers **4h1** : **4h2** was 1 : 1.3 (see ESI pages S17 and S18†). The cobalt catalysed azide decomposition of **3a** using Sugbok Chang's catalyst and conditions[26] did not give the desired product (see ESI page S23†). This is probably due to the coordination of the nitrile group to the Co atom in the complex.

The properties of the catalyst and the reaction conditions were checked on standard published substrates to avoid any error in catalyst preparation or reaction performance. To test

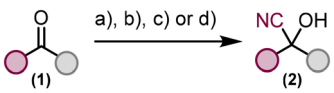

Fig. 2 Methods for cyanohydrin formation from ketones: (a) I. $NaHSO_3$, H_2O, 45 °C, 10 min; II. KCN, 10 °C–24 °C, 10 min; III. 24 °C, 16 h; (b) I. CO_2, EtOH, 24 °C, 10 min; II. KCN, 24 °C, 15 min; III. ketone addition, 24 °C, 18 h; (c) $Me_3SiCN/BF_3{\cdot}Et_2O$, DCM, 24 °C, 2 h; (d) Me_3SiCN, phosphorus ylide as a catalyst (0.1 mol%), MeCN, 24 °C.

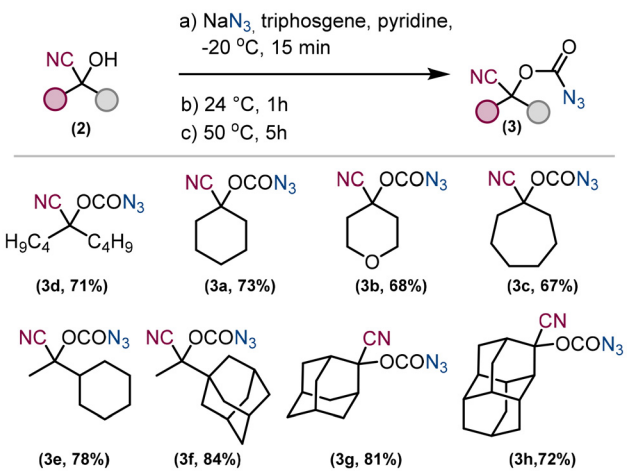

Fig. 3 Preparation of carbonazidates from cyanohydrins.

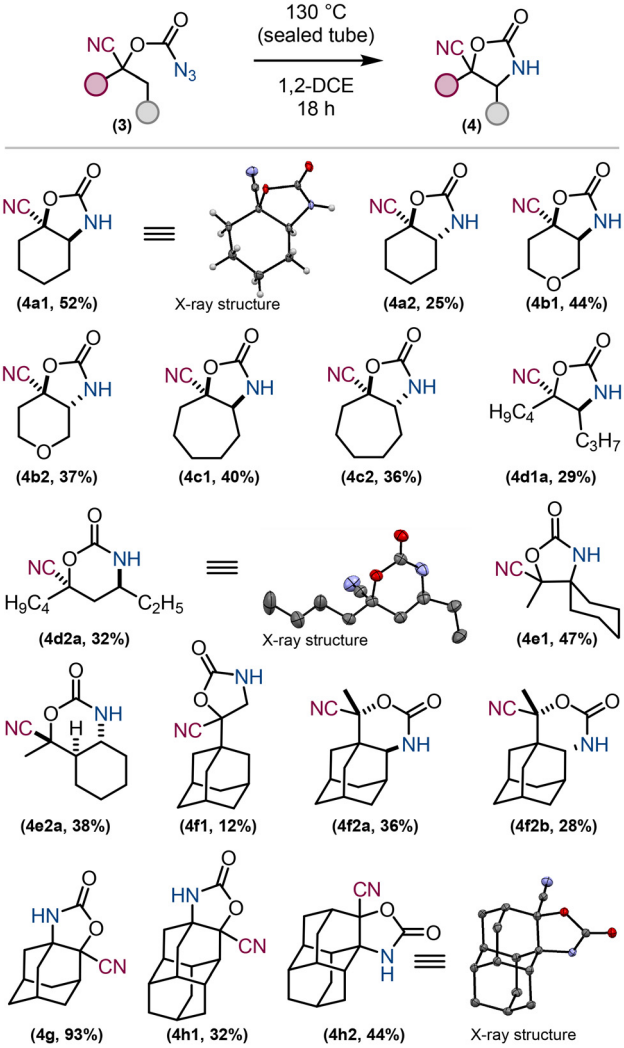

Fig. 4 Amination reaction towards cyclic carbamates. All depicted compounds in the table were isolated and characterised.

another catalytic approach to the preparation of cyclic carbamates, adamantan-2-one was converted to a cyanohydrin derivative and the resulting OH group was then converted to carbamate **13** (–$OCONH_2$ group) (see ESI page S22†). Using compound **13** as a starting material, we tested typical conditions for dirhodium catalysed nitrenoid transfer (see ESI page S22†), generating the nitrene by oxidation of the $OCONH_2$ group with $PhI(OAc)_2$. Again, the reaction did not proceed to give the desired product for the same reason, coordination of the nitrile to the rhodium atom, which deactivates the catalyst.

The amination reactions were then all carried out thermally and the results are summarised in Fig. 4. The thermal reaction of **3a** gave two diastereomers **4a1** and **4a2** in good yields. These isomers were separated by column chromatography on silica gel and their structures elucidated. The structure of **4a1** was confirmed by X-ray crystallography. The thermal decomposition of tetrahydropyran derivative **3b** resulted in a complete conversion to a mixture of diastereomers **4b1** and **4b2** in a ratio of 1 : 0.8. These isomers were separated and characterised. The cycloheptane derivative **3c** underwent the same transformation to give the isomers **4c1** and **4c2** in a ratio of 1 : 0.9. The acyclic derivative **3d** gave a mixture of 4 compounds, two diastereomers of the 5-membered carbamate derivative **4d1a** and **4d1b** in the ratio 1 : 0.6 and two diastereomers of the 6-membered carbamate derivative **4d2a** and **4d2b** in the ratio 1 : 0.4. The structure of **4d2a** was confirmed by X-ray crystallography. We then subjected the derivative **3e** containing primary, secondary and tertiary C–H groups to thermal decomposition. The reaction gave a mixture of 5 isomers, five-membered carbamate derivative **4e1** and four isomers of the six-membered carbamate derivative **4e2**. The isomer **4e2a** was isolated and its structure confirmed by 2D-NMR. A similar substrate **3f** with an adamantyl group instead of the cyclohexyl group (substrate **3e**) provided a mixture of three compounds: the five-membered carbamate **4f1**, as a result of nitrene insertion into the C–H bond of the methyl group (isolated in 12% yield) and two diastereomers of the six-membered carbamates **4f2a** and **4f2b** in a ratio of 1 : 0.8. These isomers were separated and characterised (their relative configuration was not determined). Finally, non-enolizable ketone derived substrates **3g** and **3h** were selected. Thermal decomposition of the adamantane derivative **3g** afforded the insertion product **4g** in high isolated yield. Thermal decomposition of the diamantane derivative **3f** yielded two products (regioisomers) as a result of nitrene insertion to the C–H bond in the apical position, **4h1**, and in the belt position, **4h2**. The structure of product **4h2** was confirmed by X-ray crystallography. These results (regio- and diastereo-selectivity) reflect the high reactivity of the generated nitrene species (singlet and triplet) and low differences in dissociation energies of neighbouring C–H bonds. The synthesis of structurally diverse oxazolidinones bearing tetra-substituted carbon atoms is still considered to be a challenge.[34]

Model compound **4a1** was chosen to demonstrate the cleavage of the carbamate moiety (Fig. 5). Under acidic hydrolysis conditions, compounds **4** can be converted to α-hydroxy, β-amino carboxylic acid derivatives **5** and under basic hydrolysis conditions to α-amino ketones **6**. To avoid side hydrolysis of the nitrile, **4a1** was first protected with Boc to allow carbamate cleavage under milder hydrolysis conditions. Boc protection of an amino group also prevents undesired self-condensation reactions of an α-amino ketone.

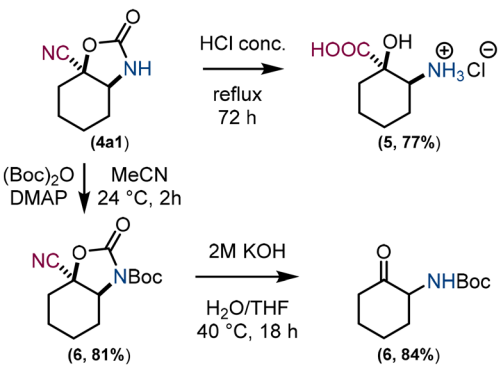

Fig. 5 Cleavage of the carbamate group using acidic and basic hydrolysis.

Our new approach to amino ketones was demonstrated using the natural compound estrone (Fig. 6). The commercially available *O*-methyl estrone derivative **7** was converted to the cyanohydrin derivative **8**. In the next step, the hydroxy group of the cyanohydrin derivative **8** was converted to carbonazidate **9**.

Carbonazidate derivative **9** was used in the thermal nitrene insertion reaction to give a mixture of two insertion products – the six-membered carbamate **10a** as a result of nitrene insertion into the C(12)–H bond and the five-membered carbamate **10b** as a result of nitrene insertion into the C(16)–H bond in a 1 : 1 ratio. The formation of the corresponding diastereomers

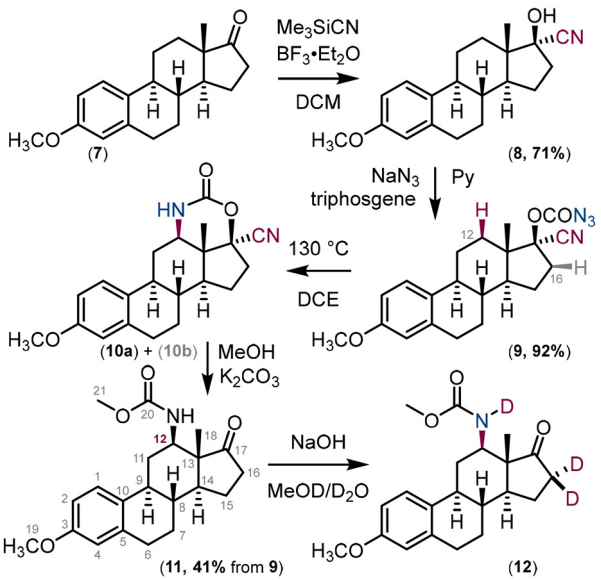

Fig. 6 Synthesis of the C(12) *N*-substituted estrone derivative **11**. Compound **10b** is a result of nitrene insertion into the C(16)–H bond.

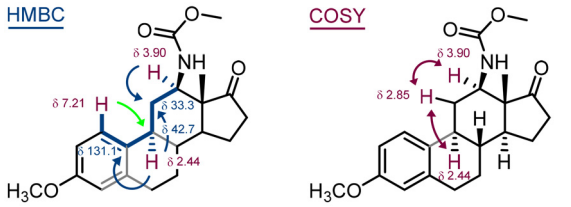

Fig. 7 2D-NMR structure elucidation of the estrone derivative **11**. HMBC 2-bond cross peaks are given in blue and the 3-bond cross peak is shown in green. Coupled hydrogens in COSY spectra are shown in red.

(for **10a** and **10b**) was not observed presumably due to the rigidity of the steroid structure. The mixture of inseparable (by column chromatography) isomers was used in the next step, the methanolysis of the carbamate under basic conditions. The major product **11** was isolated in 41% yield and its structure elucidated using 2D-NMR techniques (Fig. 7). Deuterium exchange of the acidic hydrogens in compound **12** confirmed the structure of the final compound **11**. It is important to note that C(12) substitution reactions of estrone derivatives have so far been limited to copper-mediated hydroxylation reactions.[35–39] Carbonazidates derived from C(17) alcohol, *i.e.* C(17)H–OCON$_3$, yield ketone as the main product after hydrolysis, as the nitrene insertion reaction proceeds preferentially at the C(17)–H bond.[27]

In conclusion, we have developed a new protocol for the amination of enolizable and non-enolizable ketones. This method can also be used for the synthesis of various other compounds derived from cyclic carbamates attached to the α-position of nitriles.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its ESI.† The ESI includes experimental procedures, compound descriptions, X-ray data and copies of NMR spectra.

Conflicts of interest

There are no conflicts to declare.

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