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Aryne insertion into α-cyanocarbonyl compounds: direct introduction of carbonyl and cyanomethyl moieties into the aromatic skeletons

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Abstract—Two different carbon functional groups can be introduced simultaneously into 1,2-positions of aromatic skeletons based upon a novel insertion reaction of arynes into a carbonyl–cyanomethyl σ-bond of α-cyanocarbonyl compounds.

Insertion reactions of arynes[1] into a nucleophilic–electrophilic σ-bond have engaged much attention as unique straightforward methods for synthesis of substituted arenes, in which two functional groups are introduced into the adjacent positions of the aromatic skeletons. In this context, we have already reported the insertion reactions into a nitrogen–carbonyl,[2] sulfur–tin[3] or nitrogen–silicon[4] σ-bond, and furthermore, even a carbon–carbon σ-bond has been found to be applicable to the reaction by the use of β-dicarbonyl compounds, enabling two carbon–carbon bond-forming processes to take place simultaneously.[5–7] Since then we have been studying the reactions of arynes with other active methylene compounds, and have found that α-cyanocarbonyl compounds add across arynes at their carbonyl–methylene moieties exclusively under very mild conditions. Herein, we disclose that carbonyl and cyanomethyl moieties can be efficiently introduced into 1,2-positions of aromatic skeletons depending upon the novel carbon–carbon σ-bond-addition reaction (Eq. 1).[8]

(1)

First the reaction of benzyne, prepared in situ from 2-(trimethylsilyl)phenyl triflate (**1a**)[9] and a fluoride ion (KF/18-crown-6), with pivaloylacetonitrile (**2a**) was conducted in THF at room temperature to afford an 82% yield of *tert*-butyl 2-(cyanomethyl)phenyl ketone (**3aa**) (Scheme 1). The reaction occurred exclusively at the carbonyl–methylene bond, and a product arising from insertion into the cyano–methylene bond did not form at all.[10] The reaction was also applicable to 2,3-naphthalyne (from **1b**) or 4,5-dimethylbenzyne (from **1c**), giving the respective insertion products (**3ba** or **3ca**) in high yields. A cyclopentene- or cyclohexene-condensed aryne (from **1d** or **1e**) underwent the addition to furnish excellent yields of the products (**3da** or **3ea**), and furthermore, 3,6-dimethoxybenzyne (from **1f**) reacted smoothly with **2a** irrespective of its steric congestion around the triple bond. Facile insertion of 3-methoxybenzyne (from **1g**) was observed as well to provide **3ga** as the sole product, bearing the cyanomethyl moiety at the *meta* position of the methoxy group. In marked contrast, the reaction of 4-methylbenzyne (from **1h**) produced a mixture of regioisomeric products (**3ha** and **3′ha**) in the ratio of 50:50, which implies that the present reaction certainly proceeds through an aryne intermediate.

We next investigated the reaction of other α-cyanocarbonyl compounds (Scheme 2). Thus, when benzoylacetonitrile (**2b**) or propanoylacetonitrile (**2c**) was treated with benzyne, the respective insertion product (**3ab** or **3ac**) was produced in 63% or 57% yield, being accompanied by the formation of a 2:1 coupling product (**4ab** or **4ac**), which holds the phenyl moiety at the

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Keywords: Arynes; Carbon–carbon σ-bond cleavage; α-Cyanocarbonyl compounds; Insertion reactions.

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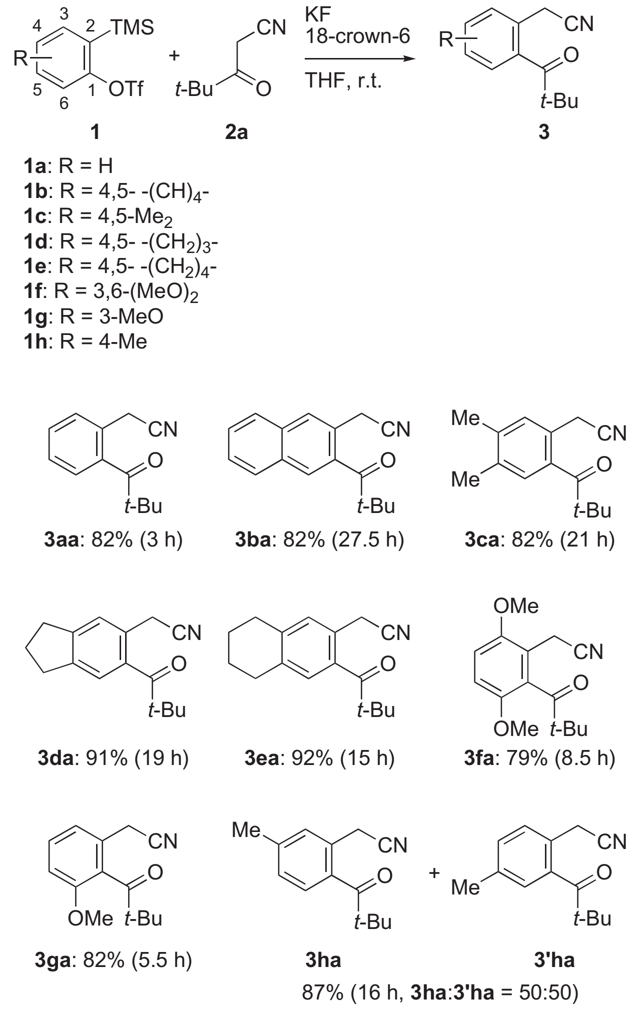
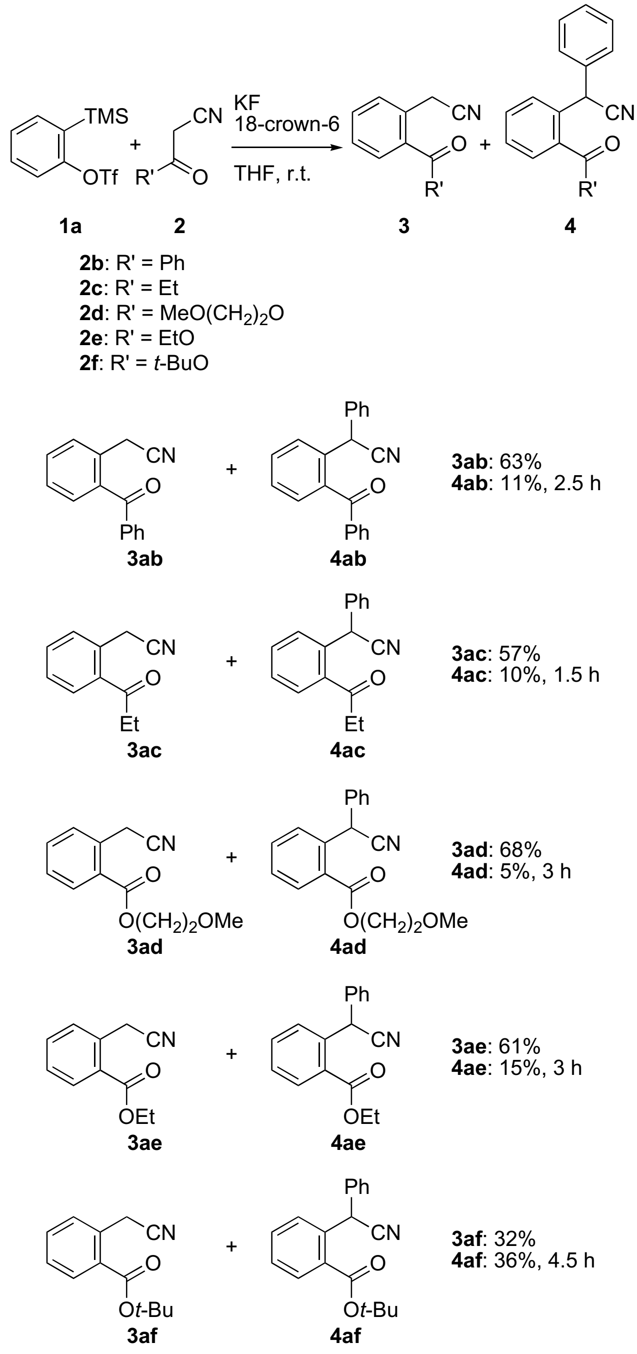


Scheme 1.

benzylic position. A methoxyethyl (**2d**), ethyl (**2e**) or *tert*-butyl (**2f**) ester of cyanoacetic acid also took part in the reaction, providing a mixture of the 1:1 product (**3ad**–**3af**) and the 2:1 product (**4ad**–**4af**).[11]

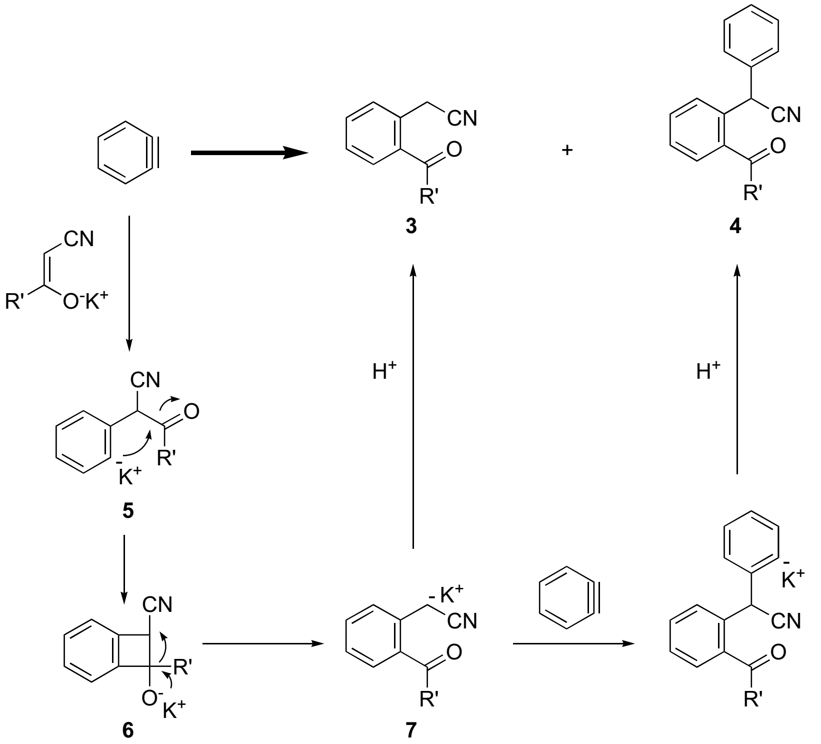
A plausible pathway of the insertion reaction is described in Scheme 3. First, an in situ-generated enolate attacks an aryne to afford aryl anion **5**, which then undergoes intramolecular nucleophilic substitution at a carbonyl moiety, giving benzyl anion **7** via benzocyclobutene **6**.[12] Proton abstraction of **7** furnishes **3**, while 2:1 product **4** arises from the reaction of **7** with a second aryne. The perfect regioselectivity observed in the reaction of 3-methoxybenzyne can be rationally explained by a steric and/or electron-withdrawing effect of the methoxy group, both of which favor the nucleophilic attack at *m*-position of the substituent. In the case of 4-methylbenzyne, steric and electronic differences around the triple bond would be so slight that an equal addition to the both ends takes place, leading to the formation of a mixture of regioisomers.



Scheme 2.

In conclusion, we have demonstrated that two different carbon functional groups, carbonyl and cyanomethyl groups, can directly be introduced into adjacent positions of aromatic skeletons based upon the novel carbon–carbon σ-bond-addition reaction to arynes. Further studies on synthetic applications to other active methylene compounds are in progress.

General procedure: To a THF solution (4.0 mL) of 18-crown-6 (0.127 g, 0.48 mmol), **1** (0.24 mmol) and **2** (0.20 mmol) was added KF (0.028 g, 0.48 mmol), and the resulting mixture was stirred at room temperature. After the time specified in Schemes 1 and 2, the solvent was removed in vacuo. Silicagel column chromatography (dichloromethane as an eluent) gave the corresponding product.



Scheme 3.

Acknowledgements

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