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Facile synthesis of 2-nitromethyl aromatic ketones by insertion of benzynes into the C-C bond of α -nitroketones

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ABSTRACT

A facile method to synthesize 2-nitromethyl aromatic ketones was developed. In the method, benzyne was generated in situ for the insertion to α -Nitroketones in one pot to achieve 2-nitromethyl aromatic ketones under mild conditions. Aromatic and aliphatic α -nitroketones were applied in the reaction, and the results show that aliphatic α -nitroketones gave excellent yields (up to 96%), while aromatic α -nitroketones gave moderate yields. The synthesized 2-nitromethyl aromatic ketones could be potential substrates to synthesize isoindoles.

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KEYWORDS

2-Nitromethyl aromatic ketone; α-nitroketone; benzyne; inserion

GRAPHICAL ABSTRACT



Introduction

Arynes are highly strained and kinetically unstable molecules that have been recognized as useful reactive intermediates in organic synthesis.^[1] Insertion of arynes into an element-element σ -bond has high synthetic significance, because both elements can be introduced into the adjacent positions of aromatic skeletons simultaneously, leading to the formation of polysubstituted arenes, which are otherwise difficult to prepare.^[2] Many works for insertion of arynes into a heteroatom-carbon σ -bond under mild conditions had been reported,^[3] while examples of arynes insertion into a carbon-carbon σ -bond are rare. In 2005, Tamber and Stoltz reported the first example of acyl-alkylation of arynes with β -ketoesters, which is an efficient method for the generation of interesting ortho-disubstituted arenes and benzannulated carbocycles.^[4] Afterwards, they applied

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^aReaction conditions: 0.4 mmol α -nitroketones, 1.25 equiv of benzyne precursor and 2.5 equiv of flouride in 4 ml of solvent at selected temperature for 8 h.

^blsolated yield.

this technology for the synthesis of natural product (+)-amurensinine successfully.^[5] Subsequently, Kunai et al. disclosed that the carbon-carbon σ -bond of β -dicarbonyl compounds also readily added to arynes to form two carbon-carbon σ -bonds in one step, which enables direct introduction of different carbon functional groups into adjacent positions of the aromatic skeleton, and provides diverse polysubstituted arenes straightforwardly^[6].

Herein, we report the insertion of benzynes into carbon-carbon σ -bond of α -nitroketones, which is a straightforward method for the synthesis of various 2-nitromethylphenyl ketones that could be potential substrates to prepare isoindoles.

Results and discussion

The reaction of 2-nitro-2-phenylethanone 2a with benzyne was invstigated, in which, *ortho*-(trimethylsilyl) phenyl triflate 1a was used as benzyne precursor. The reaction was carried out in acetonitrile or THF, and various fluoride salts were screened to generate benzyne in situ. The results show that KF was the most suitable reagent among $[Bu_4N]F$, NaF, CsF and KF (Table 1, entries 1–7), and acetonitrile is better solvent than THF (Table 1, entries 6 and 8).

With the optimized conditions, the scope and the limitation of this reaction was examined. The results shown in Table 2 demonstrate that the reaction could proceed smoothly with wide range ketones. Alkylketones (2g-2i) added to benzyne afforded insertion products in excellent yields (Table 2, entries 7-9). Arylketones (2a-2f) added to benzyne in moderate to good yields. Unsubstituted aryl ketones (2b-2e) provided relatively low yields (Table 2, entries 2–5). Furthermore, substituted benzyne could also insert into α -nitroketones. When 4, 5-dimethyl-1-(trimethylsilyl) phenyl triflate 1b was selected as substrate to react with ketones 2g, 2h and 2i, the insertion products 3bg, 3bh and 3bi were obtained in good yields (Table 2, entries 10, 11 and 12).

	R TMS R OTf +	O R ₁ NO ₂ KF, 80°C CH ₃ CN, 8h	$\begin{array}{c} R \\ R \\ R \\ \end{array} \\ R \\ 3 \\ \end{array} \\ \begin{array}{c} O \\ R_1 \\ NO_2 \\ \end{array} \\ \begin{array}{c} O \\ R_1 \\ NO_2 \\ \end{array} \\ \end{array}$	
Entry ^a	R(1)	R ₁ (2)	3	Yield (%) ^b
1	H (1a)	Ph (2a)	3aa	71
2	Н	m-BrC ₆ H ₄ (2b)	3ab	59
3	Н	$o-BrC_6H_4$ (2c)	3ac	33
4	Н	$p-FC_6H_4$ (2d)	3ad	61
5	Н	$p-MeOC_6H_4$ (2e)	3ae	31
6	Н	2-Furanyl (2f)	3af	75
7	Н	Ethyl (2g)	3ag	95
8	Н	<i>n</i> -Pr (2h)	3ah	93
9	Н	Cyclohexyl (2i)	3ai	96
10	Me (1b)	Ethyl (2g)	3bg	84
11	Me	<i>n</i> -Pr (2h)	3bh	83
12	Ме	Cyclohexyl (2i)	3bi	80

Table 2. Reaction of benzynes with α -nitroketones.

^aReaction conditions: 0.4 mmol α -nitroketones, 1.25 equiv of benzyne precursor and 2.5 equiv of KF in 4 mL of CH₃CN at 80 °C for 8 h.

^blsolated yield.



R1 =Allkyl, Aryl

Scheme 1. A proposed method for the synthesis of isoindole derivatines.



Scheme 2. A plausible mechanism for the reaction of benzyne with α -nitroketones.

The produced 2-nitromethylated phenylketones **3** could be very useful building blocks. As depicted in Scheme 1, via selective reduction nitro group of nitro ketones^[7] and intramolecular condensation^[8] respectively, which would afford a new method for the synthesis of isoindole derivatives.

A plausible mechanism of the insertion is described in Scheme 2. Firstly, nucleophilic attack of an enolate 4 to the benzyne occurs to produce an aryl anion 5, which then undergoes intramolecular nucleophilic attack to the carbonyl moiety, giving the benzo-cyclobutane 6. Ring opening of the resulting benzocyclobutane 6 affords benzyl anion 7 and a proton abstraction by 7 from water gives the product 3.

Conclusion

We have demonstrated that the carbon-carbon σ -bond of various α -nitroketones can be readily cleaved and added to the carbon-carbon triple bond of benzynes under mild conditions. The transformation results in the formation of 2-nitromethyl aromatic ketones directly that would otherwise be difficult to obtain. A further study on converting the insertion products **3** to isoindoles is proceeding.

Experimental

Commercial reagents were used as received. Benzyne precursor ortho-(trimethylsilyl) phenyl triflate **1a** was purchased from the Sigma-Aldrich Chemical Company. Substituted benzyne precursor 4, 5-dimethyl-1-(trimethylsilyl) phenyl triflate **1b** was prepared according to literature procedures.^[9] Preparation of α -nitroketones (**2a–2i**) could be found in supporting information. CH₃CN was distilled from CaH₂. ¹H NMR spectra were recorded on a Brucker Avance 300MHz. ¹H and ¹³C NMR (300 and 75MHz, respectively) spectra were recorded in CDCl₃. ¹H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard (CDCl₃, d=7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ¹³C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard (CDCl₃, d=77.00 ppm). High resolution mass spectra were recorded on Aligent 6230 TOF LC/MS.

General procedure for the insertion reaction

To a flame-dried sealed tube was charged with anhydrous acetonitrile (4 mL), α -nitroketone **2** (0.4 mmol), benzyne precursor **1a** or **1b** (0.5 mmol, 1.25 equiv) and potassium fluoride (75 mg, 1.0 mmol, 2.5 equiv) sequentially. The mixture was then heated at 80 °C till benzyne precursor **1a** or **1b** was consumed completely. After completion of the reaction, the mixture was quenched with brine (4 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The organic phases were combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude product, which was subjected to flash chromatography for further purification.

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