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Synthesis of Trifluoromethylated Cycloheptatrienes from *N*-Tosylhydrazones: Transition-Metal-Free Büchner Ring Expansion

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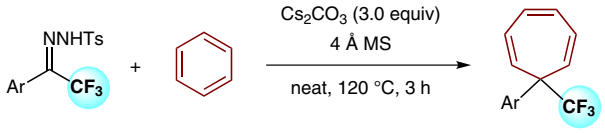


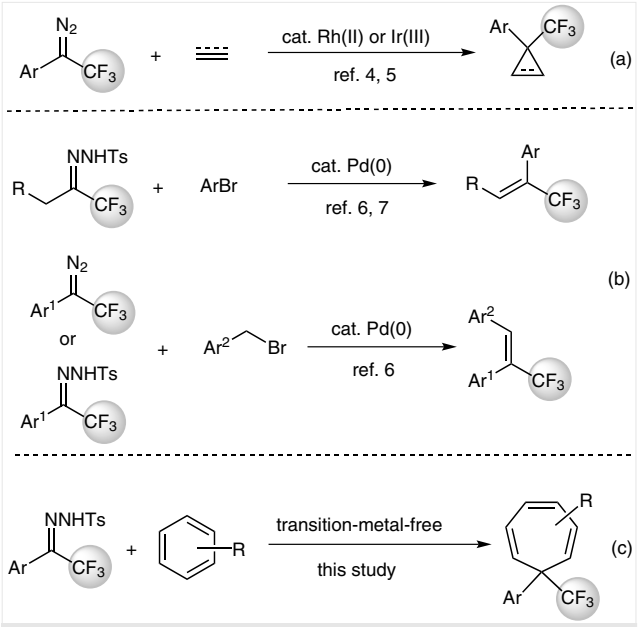
Received: 30.09.2014
Accepted after revision: 21.10.2014
Published online: 18.11.2014
DOI: 10.1055/s-0034-1378937; Art ID: st-2014-u0823-c

Abstract A transition-metal-free Büchner reaction using trifluoromethylated *N*-tosylhydrazones as substrates is reported. A series of trifluoromethylated cycloheptatriene derivatives can be synthesized by this straightforward method.

Key words diazo compounds, carbene, trifluoromethylation, Büchner reaction, cycloheptatriene

Trifluoromethyl-bearing organic molecules have found wide applications in pharmaceuticals, agrochemicals, and functional materials.[1] However, trifluoromethyl-bearing organic molecules do not exist in the nature. Consequently, it is highly important to develop general and practical methods to synthesize trifluoromethyl-bearing compounds. Great efforts have devoted to this area and significant progress has been made in recent years.[2]

On the other hand, diazo compounds possess diverse reactivities and are highly useful in organic synthesis. In particular, diazo compounds have found extensive applications as metal carbene precursors in transition-metal-catalyzed reactions.[3] Thus, the diazo compounds bearing the trifluoromethyl group have become attractive for the synthesis of trifluoromethyl-containing organic compounds. For example, transition-metal-catalyzed cyclopropenation and cyclopropanation with 1-aryl-2,2,2-trifluorodiazoethanes have been reported by Davis[4] and Katsuki,[5] respectively (Scheme 1, a). Recently, we[6] and Valdés[7] have independently reported the palladium-catalyzed cross-coupling reaction with 1-aryl-2,2,2-trifluoro ketone and 1-alkyl-2,2,2-trifluoro ketone *N*-tosylhydrazones. The diazo compounds could be generated in situ in these cases.[8] These reactions provide unique methods for the synthesis of trifluoromethylated alkenes and dienes (Scheme 1, b).



Scheme 1 Reactions with trifluoromethyl-bearing diazo compounds or *N*-tosylhydrazones

In connection to our interest in both carbene chemistry and trifluoromethylations, herein we report a transition-metal-free Büchner reaction using trifluoromethylated *N*-tosylhydrazones as the substrates (Scheme 1, c). The rhodium(II)-catalyzed intramolecular Büchner reaction as an effective approach toward seven-membered carbocycles have been extensively studied by the groups of McKervey, Doyle, Moody, and others.[9] The intermolecular Büchner reaction without transition-metal catalysis usually suffers low selectivity due to other competing reaction pathways.[3b] The Büchner reaction with 1-aryl-2,2,2-trifluorodiazoethanes reported herein is not interfered by the aromatic sp^2 C–H

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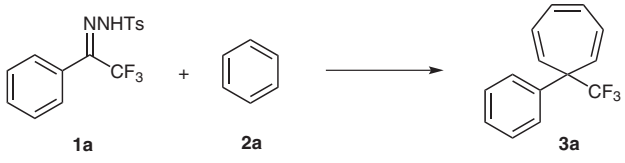
insertion side reactions, thus providing a convenient method for the synthesis of trifluoromethylated cycloheptatrienes.

The initial study was carried out with *N*-tosylhydrazone **1a** (0.2 mmol) and benzene (**2a**, 2.0 mL) as the substrates, with Cs_2CO_3 (3.0 equiv) as the base at 80 °C. After three hours, the product **3a** was isolated in 23% yield (Table 1, entry 1). To our delight, the direct C–H insertion product was not detected.[10] Next, the effect of temperature was examined. The yield could be slightly improved at high temperature (Table 1, entry 2). It was found that adding 4 Å molecular sieves (4 Å MS) as additive could further improve the yield (Table 1, entries 4 and 5). Besides, the concentration has marginal effect on the reaction (Table 1, entries 4–9). Finally, the effect of base was studied, and Cs_2CO_3 was found to afford the best result (Table 1, entries 10–14).

Table 1 Optimization of Reaction Conditions[a]



1a **2a** **3a**

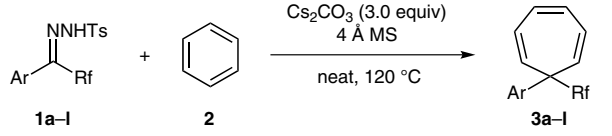
Entry	Base (equiv)	Additive	Temp (°C)	**2a** (mL)	Yield (%)[b]
1	Cs_2CO_3 (3)	none	80	2	23
2	Cs_2CO_3 (3)	none	110	2	33[c]
3	Cs_2CO_3 (3)	4 Å MS	80	2	33[c]
4	Cs_2CO_3 (3)	4 Å MS	120	2	42
5	Cs_2CO_3 (3)	4 Å MS	80	1	20[c]
6	Cs_2CO_3 (3)	4 Å MS	120	3	51
7	Cs_2CO_3 (3)	4 Å MS	120	4	61
8	Cs_2CO_3 (3)	4 Å MS	120	5	51
9	Cs_2CO_3 (3)	4 Å MS	120	10	57
10	K_2CO_3 (3)	4 Å MS	2	2	25[c]
11	LiO*t*-Bu (3)	4 Å MS	4	4	30[c]
12	NaO*t*-Bu (3)	4 Å MS	4	4	55[c]
13	KO*t*-Bu (3)	4 Å MS	4	4	49
14	K_3PO_4 (3)	4 Å MS	4	4	53

[a] The reaction was carried in 0.2 mmol scale with 4 Å MS (50 mg). Reaction time is 3 h and the substances were reacted at a sealed tube.
[b] Unless otherwise noted, it refers to isolated yield.
[c] Yield determined by GC–MS.

With the optimized reaction conditions (Table 1, entry 7), the substrate scope of the reaction was investigated by using a series of *N*-tosylhydrazones.[11] As illustrated in Table 2, a variety of *N*-tosylhydrazones **1a**–**l** bearing different substituents on the aromatic rings were reacted smoothly with benzene, affording the desired products in moderate yields (**3a**–**l**). *N*-Tosylhydrazones bearing halogen substituents, such as fluoro, chloro, bromo, and iodo, all give the corresponding products in decent yields. In particular, active iodide **1e** is compatible under the reaction conditions (Table 2, entry 5). The substrates bearing electron-withdrawing substituents, such as nitro and trifluoromethyl, gave the corresponding products in moderate yields (Table 2, entries 7 and 8).

However, the substrate with strong electron-donating 4-methoxy substituent only gave the product in low yield (Table 2, entry 11). Notably, the reaction also worked well with the substrate bearing the $CF_2CF_2CF_3$ group instead of the trifluoromethyl group (Table 2, entry 12). The reaction seems to be significantly affected by the steric effect of the substituent, as the substrate bearing the 2-methyl group gave only trace amount of the expected product (Table 2, entry 13).

Table 2 Scope of *N*-Tosylhydrazones



1a–l **2** **3a–l**

Entry	Substrate **1a–l**	Ar	R_f	Yield (%)[a]
1	**1a**	Ph	CF_3	**3a** 61
2	**1b**	4-FC_6H_4	CF_3	**3b** 57
3	**1c**	4-ClC_6H_4	CF_3	**3c** 67
4	**1d**	4-BrC_6H_4	CF_3	**3d** 68
5	**1e**	4-IC_6H_4	CF_3	**3e** 62
6	**1f**	2-BrC_6H_4	CF_3	**3f** 64
7	**1g**	4-$F_3CC_6H_4$	CF_3	**3g** 69
8	**1h**	3-$O_2NC_6H_4$	CF_3	**3h** 56
9	**1i**	4-MeC_6H_4	CF_3	**3i** 52
10	**1j**	2-naphthyl	CF_3	**3j** 51
11	**1k**	4-$MeOC_6H_4$	CF_3	**3k** 27
12	**1l**	4-FC_6H_4	C_3F_7	**3l** 52
13	**1m**	2-MeC_6H_4	CF_3	**3m** trace

[a] Isolated yield.

Furthermore, we proceeded to expand the substance scope of arenes and examined the reactions in several aromatic solvents. In these cases, the reaction will meet the

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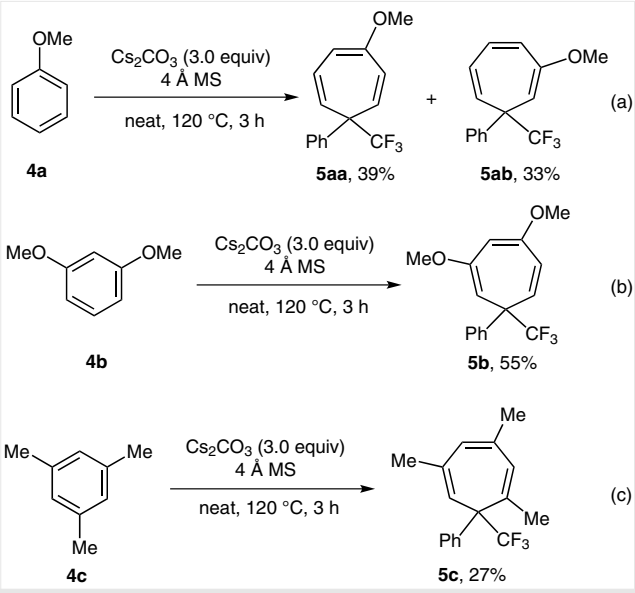
problem of regioselectivity. Three aromatic solvents have been examined: anisole (**4a**), 1,3-dimethoxybenzene (**4b**), and mesitylene (**4c**).

In the case of anisole (**4a**), two regiosomeric products **5aa** and **5ab** were isolated in approximately equal amount (Scheme 2, a). For 1,3-dimethoxybenzene (**4b**), attributed to the steric effects, the formal C–C bond insertion only occurs at the sterically less hindered sites, giving **5b** as the sole product in moderate yield (Scheme 2, b). For the symmetric substrate mesitylene (**4c**), the reaction afforded the expected product **5c**, but in 27% yield due to steric hindrance (Scheme 2, c).



Scheme 2

In summary, we have reported herein the first Büchner reaction using *N*-tosylhydrazones as the substrates. This transition-metal-free reaction afforded trifluoromethylated cycloheptatrienes in moderate yields without aromatic sp^2 C–H bond insertion by-products. This reaction demonstrates the unique reactivity of free carbene that is substituted by trifluoromethyl group. This property may be further explored for the synthesis of trifluoromethyl-containing molecules.

Acknowledgment

The project is supported by the National Basic Research Program of China (973 Program, No. 2012CB821600) and the Natural Science Foundation of China (Grant 21272010 and 21332002).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378937.

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(11) **General Procedure for the Büchner Reaction**

In an oven-dried 20 mL Schlenk tube, *N*-tosylhydrazone (**1**, 0.2 mmol, 1.0 equiv), Cs_2CO_3 (0.6 mmol, 3 equiv), and 4 Å MS were added. Then the tube was sealed with a septum, and degassed by alternating vacuum evacuation and nitrogen backfill (3×) before benzene (4 mL) was added. The reaction was then stirred at 120 °C for 3 h. The reaction mixture was cooled to r.t. and filtered through a short plug of silica gel with Et_2O as eluents. Solvent was then removed in vacuo to leave a crude mixture, which was purified by preparative TLC to afford pure products.

7-Phenyl-7-(trifluoromethyl)cyclohepta-1,3,5-triene (3a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 7.4 Hz, 2 H), 7.18–7.09 (m, 3 H), 6.44–6.42 (m, 2 H), 6.30–6.28 (m, 2 H), 5.72 (d, *J* = 9.3 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.9, 130.2, 129.8, 127.8, 127.1 (q, *J* = 281.9 Hz), 126.6, 126.6, 117.3, 53.2 (q, *J* = 25.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ = –74.3 (s, 3 F). MS (EI): *m*/*z* (%) = 236 (66) [M$^+$], 215 (15), 167 (100), 165 (60), 152 (28). IR (film): 1284, 1188, 1151, 978, 687 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}F_3$ [M]$^+$: 236.0807; found: 236.0815.

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