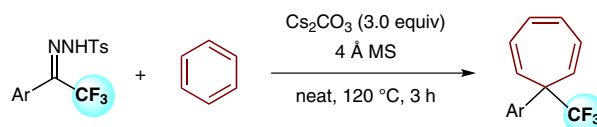


Synthesis of Trifluoromethylated Cycloheptatrienes from *N*-Tosylhydrazones: Transition-Metal-Free Büchner Ring Expansion

Zhikun Zhang^aJijie Feng^aYan Xu^aSongnan Zhang^aYuxuan Ye^aTianjiao Li^aXi Wang^{*a}Jun Chen^bYan Zhang^aJianbo Wang^{*a}

^a Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, P. R. of China
wangjb@pku.edu.cn

^b Beijing Institute of Microchemistry, No.15 Xijiangongmen Road, Haidian District, Beijing, 100091, P. R. of China

Received: 30.09.2014

Accepted after revision: 21.10.2014

Published online: 18.11.2014

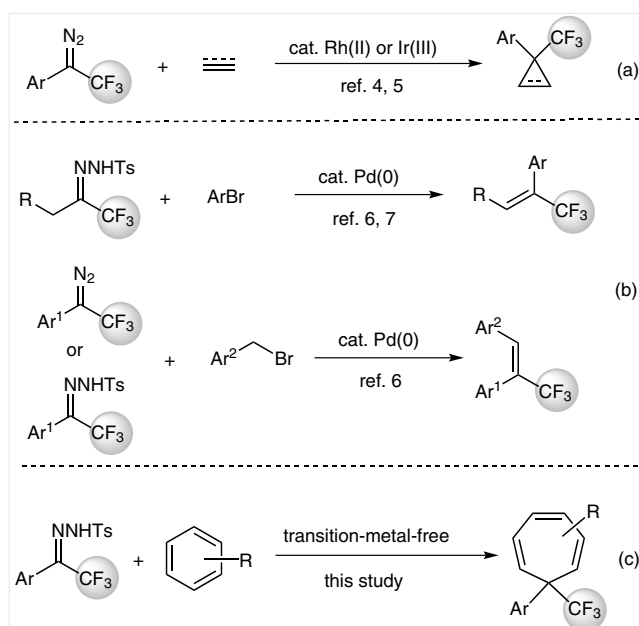
DOI: 10.1055/s-0034-1378937; Art ID: st-2014-u0823-c

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 cyclopropanation and cyclopropanation with 1-aryl-2,2,2-trifluorodiazethanes have been reported by Davis⁴ and Katsuki,⁵ respectively (Scheme 1, a). Recently, we⁶ and Valdés⁷ 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).



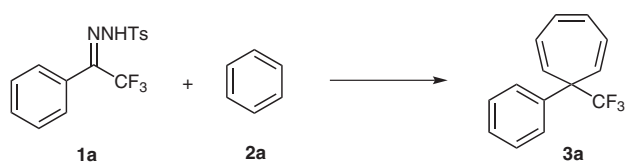
Scheme 1 Reactions with trifluoromethyl-bearing diazo compounds or *N*-tosylhydrazones

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 McKerver, 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-trifluorodiazethanes reported herein is not interfered by the aromatic sp^2 C–H

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 Cs₂CO₃ (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 Cs₂CO₃ was found to afford the best result (Table 1, entries 10–14).

Table 1 Optimization of Reaction Conditions^a



Entry	Base (equiv)	Additive	Temp (°C)	2a (mL)	Yield (%) ^b
1	Cs ₂ CO ₃ (3)	none	80	2	23
2	Cs ₂ CO ₃ (3)	none	110	2	33 ^c
3	Cs ₂ CO ₃ (3)	4 Å MS	80	2	33 ^c
4	Cs ₂ CO ₃ (3)	4 Å MS	120	2	42
5	Cs ₂ CO ₃ (3)	4 Å MS	80	1	20 ^c
6	Cs ₂ CO ₃ (3)	4 Å MS	120	3	51
7	Cs ₂ CO ₃ (3)	4 Å MS	120	4	61
8	Cs ₂ CO ₃ (3)	4 Å MS	120	5	51
9	Cs ₂ CO ₃ (3)	4 Å MS	120	10	57
10	K ₂ CO ₃ (3)	4 Å MS	2	2	25 ^c
11	LiOt-Bu (3)	4 Å MS	4	4	30 ^c
12	NaOt-Bu (3)	4 Å MS	4	4	55 ^c
13	KOt-Bu (3)	4 Å MS	4	4	49
14	K ₃ PO 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.

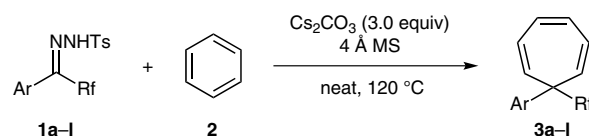
^b Unless otherwise noted, it refers to isolated yield.

^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 CF₂CF₂CF₃ 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



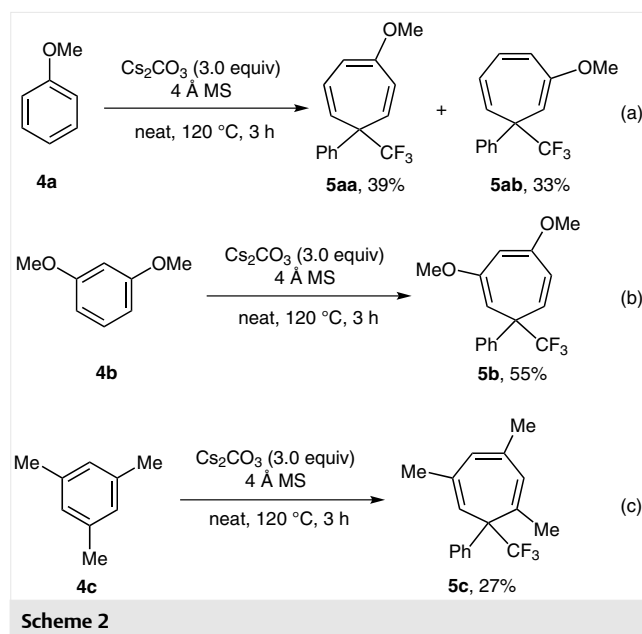
Entry	Substrate 1a–l	Ar	R _f	Yield (%) ^a
1	1a	Ph	CF ₃	3a 61
2	1b	4-FC ₆ H ₄	CF ₃	3b 57
3	1c	4-ClC ₆ H ₄	CF ₃	3c 67
4	1d	4-BrC ₆ H ₄	CF ₃	3d 68
5	1e	4-IC ₆ H ₄	CF ₃	3e 62
6	1f	2-BrC ₆ H ₄	CF ₃	3f 64
7	1g	4-F ₃ CC ₆ H ₄	CF ₃	3g 69
8	1h	3-O ₂ NC ₆ H ₄	CF ₃	3h 56
9	1i	4-MeC ₆ H ₄	CF ₃	3i 52
10	1j	2-naphthyl	CF ₃	3j 51
11	1k	4-MeOC ₆ H ₄	CF ₃	3k 27
12	1l	4-FC ₆ H ₄	C ₃ F ₇	3l 52
13	1m	2-MeC ₆ H 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

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 regioisomeric 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).



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>.

References and Notes

- (1) (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, **2004**. (b) Gladysz, J. A.; Curran, D. P.; Horváth, I. T. *Handbook of Fluorous Chemistry*; Wiley-VCH: Weinheim, **2005**. (c) Horváth, I. T. *Fluorous Chemistry*; Springer: Berlin/Heidelberg, **2011**. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature (London, U.K.)* **2011**, *473*, 470. (f) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.
- (2) For selected reviews, see: (a) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, in press; DOI: 10.1021/cr500193b. (b) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, in press; DOI: 10.1021/cr5002386. (c) Chu, L.; Qing, F.-L. *Acc. Chem. Res.* **2014**, *47*, 1513. (d) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37. (e) Chen, P.; Liu, G. *Synthesis* **2013**, *45*, 2919. (f) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214. (g) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617. (h) Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8950. (i) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Asian J.* **2012**, *7*, 1744. (j) Liu, T.; Shen, Q. *Eur. J. Org. Chem.* **2012**, 6679. (k) Macé, Y.; Magnier, E. *Eur. J. Org. Chem.* **2012**, 2479. (l) García-Monforte, M. A.; Martínez-Salvador, S.; Menjón, B. *Eur. J. Inorg. Chem.* **2012**, 4945. (m) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (n) Zheng, Y.; Ma, J.-A. *Adv. Synth. Catal.* **2010**, *352*, 2745. (o) Grushin, V. V. *Acc. Chem. Res.* **2009**, *43*, 160. (p) Cahard, D.; Ma, J.-A. *Chem. Rev.* **2008**, *108*, PR1. (q) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (r) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633. (s) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975. (t) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921. (u) Mizuta, S.; Shibata, N.; Hibino, M.; Nagano, S.; Nakamura, S.; Toru, T. *Tetrahedron* **2007**, *63*, 8521. (v) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (w) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.
- (3) For selected reviews on the reaction of diazo compounds, see: (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, **1998**. (c) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577.
- (4) Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625.
- (5) Uehara, M.; Suematsu, H.; Yasutomi, Y.; Katsuki, K. *J. Am. Chem. Soc.* **2011**, *133*, 170.
- (6) Wang, X.; Xu, Y.; Deng, Y.; Zhou, Y.; Feng, J.; Ji, G.; Zhang, Y.; Wang, J. *Chem. Eur. J.* **2014**, *20*, 961.
- (7) Jiménez-Aquino, A.; Vega, J. A.; Trabanco, A. A.; Valdés, C. *Adv. Synth. Catal.* **2014**, *356*, 1079.
- (8) (a) Barluenga, J.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486. (b) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. (c) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236.
- (9) (a) Duddeck, H.; Kennedy, M.; McKervey, M. A.; Twohig, F. M. *J. Chem. Soc., Chem. Commun.* **1988**, 1586. (b) Moody, C. J.; Miah, S.; Slawin, A. M. Z.; Mansfield, D. J.; Richards, I. C. *J. Chem. Soc.,*

Perkin Trans. 1 **1988**, 4067. (c) Doyle, M. P.; Ene, D. G.; Forbes, D. C.; Pillow, T. H. *Chem. Commun.* **1999**, 1691. (d) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (e) Cordi, A. A.; Lacoste, J.-M.; Hennig, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3. (f) Merlic, C. A.; Zechman, A. L.; Miller, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 11101. (g) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933. (h) Doyle, M. P.; Phillips, I. M. *Tetrahedron Lett.* **2001**, *42*, 3155. (i) Kane, J. L.; Shea, K. M.; Crombie, A. L.; Danheiser, R. L. *Org. Lett.* **2011**, *3*, 1081.

(10) Brunner, J.; Serin, H.; Richards, F. M. *J. Biol. Chem.* **1980**, *255*, 3313.

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

In an oven-dried 20 mL Schlenk tube, *N*-tosylhydrazone (**1**, 0.2 mmol, 1.0 equiv), Cs₂CO₃ (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 Et₂O 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)

¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (101 MHz, CDCl₃): 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). ¹⁹F NMR (470 MHz, CDCl₃): 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 C₁₄H₁₁F₃ [M]⁺: 236.0807; found: 236.0815.