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Synthesis of novel oxygen heterocycles: 1,10-dioxa-cyclopenta[*a*]fluorene and benzo[*b*]naphtho[2, 1-*d*]furans via Dötz intramolecular benzannulation

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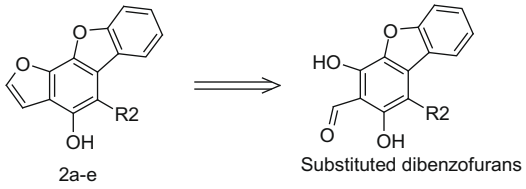
ABSTRACT

Novel fused heterocycles 1,10-dioxa-cyclopenta[*a*]fluorene and benzo[*b*]naphtho[2, 1-*d*]furans were synthesized via Dötz intramolecular benzannulation of alkyne tethered aryloxy chromium Fischer carbenes.

Myriad fused nitrogen heterocycles have been synthesized from tethered alkynyl amino carbenes by intramolecular Dötz benzannulation.[1a–e] For example, a variety of vinyl and aryl-2-alkynylcarbenes on thermolysis generate carbazoles and benzocarbazoles.[2a–c] Woodgate et al. have synthesized diterpenoid indole derivatives via tethered chromium alkynylaminocarbenes.[2d] Several reactions have also been reported for *o*-analogous carbenes, Wulff et al. and Semmelhack et al. have synthesized cyclophanes, naphthoquinones, and furanocoumarins from intramolecular Dötz Benzannulation of alkyne tethered alkoxy carbenes.[3a–d]

Recently Giese et al. have reported applications of silyl-substituted alkyne tethered aryloxy fischer carbenes for the synthesis of rocaglamide skeleton via arrested intramolecular alkyne insertion.[4a] Nakata et al. have utilized intramolecular Dötz reaction to synthesize arnebinol.[4b] In order to further demonstrate the utility of tethered aryloxy Fischer chromium carbenes toward novel oxygen heterocycles, we herein present their intramolecular benzannulation to yield heterocycles 1,10-dioxa-cyclopenta[*a*]fluorene **2a–e** and benzo [*b*] naphtho [2,1-*d*] furans **2f–i**. Compounds **2a–e** can be considered as immediate precursors of substituted dibenzofurans (Scheme 1).[5] Importance of dibenzofurans is well known, as it is present in a variety of natural products.[6a–m] This makes our oxygen fused heterocycles a very interesting target for synthesis.

Retrosynthetically we envisioned the formation of fused *o*-heterocycles via intramolecular benzannulation of fischer aryloxy carbenes **1a–i**, under thermal heating. The fischer carbenes **1a–i** can be synthesized by coupling of phenols **5a–e** with acylated complex **7**.[7] Syntheses of phenols **5a–e** were accomplished by sonogashira coupling of *o*-iodophenol with substituted alkynes.



Scheme 1. Synthetic proposal for the conversion of benzofuro [7,6-*b*][1] benzofurans to dibenzofurans.

The facile cyclization process common to *o*-hydroxy acetylenic phenols[8] thus formed was prevented by employing mild reaction conditions.[9]

Hence, *o*-iodophenols were protected followed by sonogashira coupling with corresponding alkynes and then deprotected to yield the desired *o*-hydroxy acetylenic phenols **5a–e** (Scheme 2). *o*-hydroxy acetylenic phenols **5a–e** were then employed to synthesize the *o*-alkyne tethered aryloxy Fischer carbenes **1a–i**. To synthesize the carbenes, we used Pulley's protocol, where the optimum procedure involves the formation of metal acyl complex **7a–c** (synthesized by addition of acetyl bromide to ammonium ate complex **6a–c**), followed immediately by the addition of sodium salt of *o*-hydroxy acetylenic phenols **8a–e** at 0 °C.[7] Any efforts to perform the phenolate at room temperature (according to the original protocol) resulted in an intramolecular cyclization of the phenoxide **8a–e** to generate benzofurans (Scheme 2).

Complexes **1a–i** are obtained as deep red oils by standard chromatographic techniques and are stable to storage (−4 °C) under inert atmosphere for several weeks.[11] The yields of the carbenes ranged ~50–60% (Table 1). Efforts are in progress toward optimization of the yields via crystallization.

After the synthesis of aryloxy carbenes **1a–i**, our final frontier was their intramolecular benzannulation to achieve the fused

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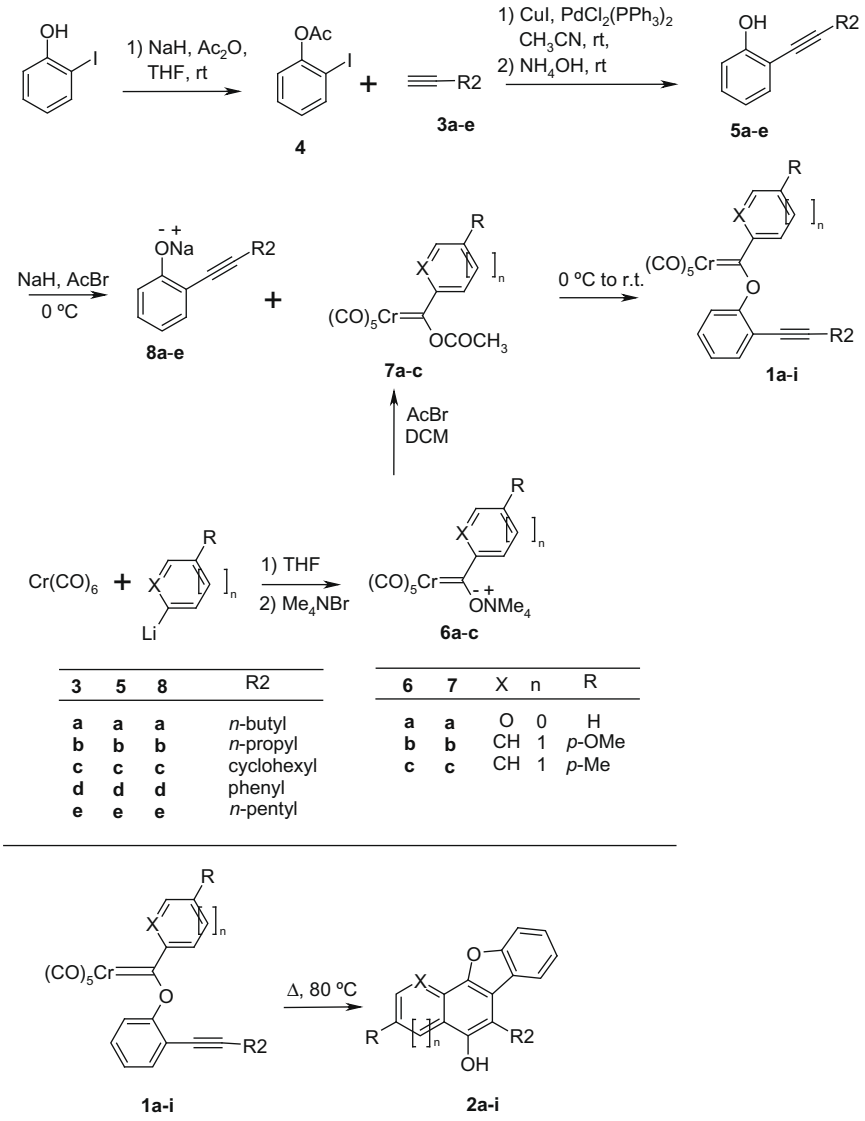


3	5	8	R2
a	a	a	*n*-butyl
b	b	b	*n*-propyl
c	c	c	cyclohexyl
d	d	d	phenyl
e	e	e	*n*-pentyl

6	7	X	n	R
a	a	O	0	H
b	b	CH	1	*p*-OMe
c	c	CH	1	*p*-Me

1a-e / **2a-e**: X = O, n = 0, R = H, R2 = *n*-butyl, *n*-propyl, cyclohexyl, phenyl and *n*-pentyl respectively.
1f-i / **2f-i**: X= CH, n = 1, R = *p*-OMe, and *p*-Me, R2 = *n*-butyl, *n*-propyl, *n*-butyl and *n*-pentyl respectively

Scheme 2. Synthesis of aryloxy fischer chromium carbenes **1a–i** and *o*-heterocycles by intramolecular Dötz benzannulation.

heterocycles. Subsequent thermolysis of **1a–i** in THF generated the desired *o*-fused heterocycles in 65–70% yield as light yellow crystalline solids (Table 2).[11] The reactions were also tried under solvent-free conditions. Till date there have been no reports, to the best of our knowledge, about conducting intramolecular Dötz reaction under solvent free conditions. The yields under solvent-free conditions are 10–15% lower (45–40%) than under solvents viz. THF (65–70%). (Table 2). The advantage in this procedure is drastic reduction of reaction time. For example, the reaction of carbene **1f** gives the *o*-heterocycle **2f** after 18 h at 60 °C in THF while solvent-free reaction goes to completion in 15 min at 80 °C. Optimizations are in progress to improve the yields. Also mandatory freeze-thaw degassing of the reaction mixture (an integral protocol of all Dötz reaction of Fischer carbenes to remove dissolved oxygen from the reaction mixture in order to prevent oxidation of the carbene) is not necessary with solvent-free conditions. We believe that this reaction follows a mechanism similar to Dötz intermolecular benzannulation.[10] But we have not conducted any mechanistic investigation toward the formation of the product.

Hence a general and mild method of forming fused *o*-heterocycle is a valuable addition to the synthetic method available to the construction of substituted dibenzofurans.

The neutral reaction conditions are particularly attractive for synthesis of these heterocycles featuring sensitive functionalities. These preliminary results provide a fundamental basis to expand this methodology and demonstrate its utility in the ultimate synthesis of substituted dibenzofurans.

Table 1
Synthesis of carbenes

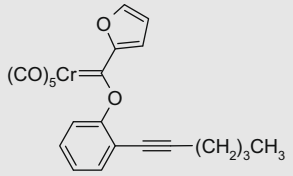
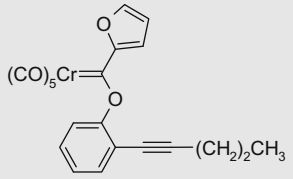
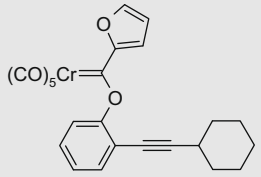
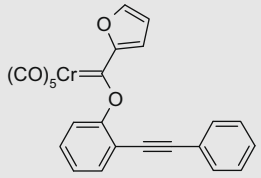
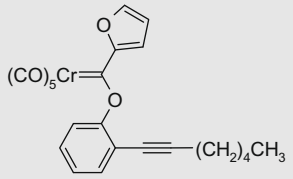
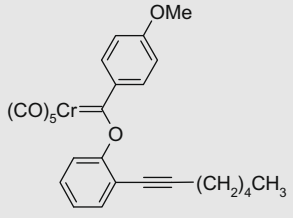
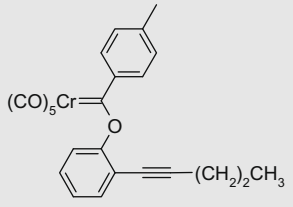
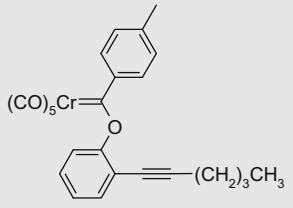
Entry	Carbenes	Yield (%)
1	 **1a**	54
2	 **1b**	51
3	 **1c**	52
4	 **1d**	50
5	 **1e**	55
6	 **1f**	57
7	 **1g**	54
8	 **1h**	57

Table 1 (*continued*)

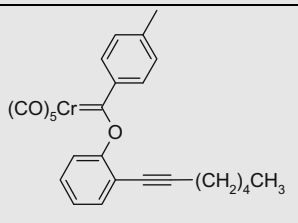
Entry	Carbenes	Yield (%)
9	 **1i**	53

Table 2
Intramolecular Dötz benzannulation

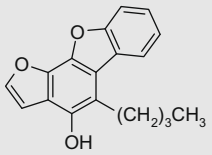
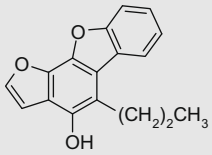
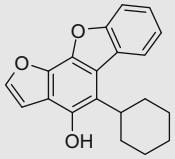
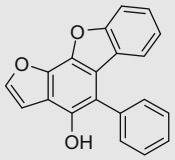
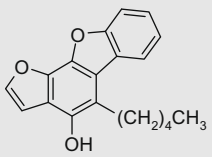
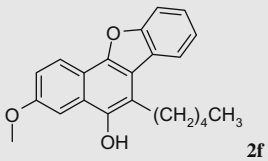
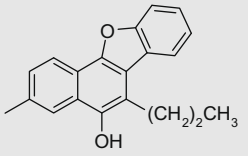
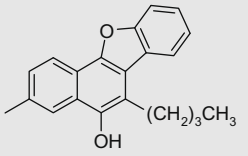
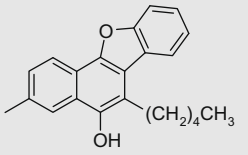
Entry	Substrate	Product	Yield (%) in solution	Yield (%) in neat
1	**1a**	 **2a**	67	41
2	**1b**	 **2b**	71	42
3	**1c**	 **2c**	56	47
4	**1d**	 **2d**	61	40
5	**1e**	 **2e**	57	46
6	**1f**	 **2f**	59	45

Table 2 (*continued*)

Entry	Substrate	Product	Yield (%) in solution	Yield (%) in neat
7	**1g**	 **2g**	51	47
8	**1h**	 **2h**	67	46
9	**1i**	 **2i**	54	47

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.123.

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11. *Spectral data of few representative new compounds*: *Pentacarbonyl [(2-hex-1-ynyl phenoxy) (furyl) carbene] chromium (0)* (**1a**) ^{1}H NMR (300 MHz, $CDCl_3$) 7.88 (s 1H), 7.42–7.35 (m, 2H), 7.26–7.23 (m, 2H), 7.12–7.11 (m, 1H), 6.60 (s, 1H), 2.12 (t, J = 6.60 Hz 2H), 1.61–1.56 (m, 2H), 1.20–1.13 (m, 2H), 0.68 (t, J = 6.90 Hz 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 12.5, 18.0, 20.8, 29.3, 74.5, 96.1, 111.8, 112.3, 118.2, 121.7, 125.7, 127.7, 132.3, 150.1, 158.3, 164.1, 215.2, 223.8.
Pentacarbonyl [(2-pent-1-ynyl phenoxy) (furyl) carbene] chromium (0) (**1b**) ^{1}H NMR (300 MHz, $CDCl_3$) 7.88 (s, 1H), 7.42–7.34 (m, 2H), 7.27–7.23 (m, 2H), 7.12–7.11 (m, 1H), 6.60 (s, 1H); 2.09 (t, J = 6.99 Hz 2H), 1.30–1.18 (m, 2H), 0.73 (t, J = 7.35 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) 11.2, 19.2, 19.6, 73.6, 94.9, 110.8, 111.2, 117.1, 120.6, 124.7, 126.7, 131.3, 149.0, 157.2, 163.1, 214.1, 222.7.
Pentacarbonyl [(2-cyclohexylethynyl phenoxy) (furyl) carbene] chromium (0) (**1c**) ^{1}H NMR (300 MHz, $CDCl_3$) 7.96 (s, 1H), 7.50–7.41 (m, 2H), 7.35–7.28 (m, 2H), 6.94 (m, 1H), 6.66 (s, 1H), 2.73–2.61 (m, 1H), 1.84–1.70 (m, 2H), 1.45–1.35 (m, 4H), 1.32–1.09 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.6, 24.9, 25.8, 29. 9, 32.1, 32.7, 74.5, 96.6, 112.9, 113.3, 114.3, 120.1, 128.8, 129.6, 131.5, 133.4, 151.1, 156.8, 165.5, 216.5, 222.2.
5-Butyl-1, 10-dioxa-cyclopenta [a] fluoren-4-ol: (**2a**) IR (KBr) ν_{max} cm^{-1}: 3274, 2955, 2855, 1664, 1466, 1346, 1040, 733; ^{1}H NMR (300 MHz, $CDCl_3$) 8.01 (d, J = 8.52 Hz, 1H), 7.78 (d, J = 9.48 Hz, 2H), 7.50–7.36 (m, 2H), 6.98 (s, 1H), 4.94 (s, 1H), 3.20 (t, J = 7.74 Hz, 2H), 1.83–1.73 (m, 2H), 1.64–1.51 (m, 2H), 1.03 (t, J = 7.26 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.3, 23.2, 26.3, 32.2, 104.5, 112.0, 116.1, 118.2, 120.5, 121.8, 122.9, 125.1, 125.9, 136.2, 138.6, 141.6, 144.4, 156.4; HRMS calcd for $C_{18}H_{16}O_3$ 281.1178; found: 281.1172, mp 128–130 °C.
5-Propyl-1,10-dioxa-cyclopenta[a]fluoren-4-ol: (**2b**) IR (KBr) ν_{max} cm^{-1} : 3280, 2960, 2840, 1634, 1458, 1374, 1035, 734; ^{1}H NMR (300 MHz, $CDCl_3$) 7.97–7.95 (d, J = 7.89 Hz, 1H), 7.66–7.63 (d, J = 10.06 Hz, 2H), 7.46–7.33 (m, 2H), 6.95 (s, 1H), 4.88 (s, 1H), 3.13 (t, J = 7.74 Hz, 2H), 1.86–1.72 (m, 2H), 1.12 (t, J = 7.35 Hz, 3H); ^{13}C NMR(75 MHz, $CDCl_3$) 14.2, 22.8, 28.2, 104.5, 112.0, 115.9, 118.2, 120.6, 121.8, 122.9, 125.1, 125.9, 136.1, 138.6, 141.7, 144.4, 156.4; HRMS calcd for $C_{17}H_{14}O_3$ 267.1021; found: 267.1014, mp 136–138 °C;
5-Cyclohexyl-1,10-dioxa-cyclopenta[a]fluoren-4-ol: (**2c**) IR (KBr) ν_{max} cm^{-1}: 3413, 2929, 2853, 1664, 1450, 1339, 1020, 752; ^{1}H NMR (300 MHz, $CDCl_3$) 8.12 (d, J = 7.35 Hz, 1H), 7.66–7.64 (d, J = 7.62 Hz, 2H), 7.47–7.34 (m, 2H), 6.92 (s, 1H), 4.92 (s, 1H), 3.70–3.62 (m, 1H), 2.19–1.86 (m, 4H), 1.69–1.43 (m, 4H), 1.29–0.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.9, 26.3, 26.9, 27.7, 31.4, 40.3, 104.2, 112.1, 119.3, 120.6, 121.1, 122.1, 122.7, 125.4, 125.8, 136.1, 138.4, 142.8, 144.5, 156.5; HRMS calcd for $C_{20}H_{18}O_3$ 306.3544; found: 306.3520, mp 151–154 °C.