Synthesis of substituted 6*H*-benzo[*c*]chromenes: A palladium promoted ring closure of diazonium tetrafluoroborates

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PII: S0040-4039(12)01795-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2012.10.038
Reference: TETL 42000

To appear in: *Tetrahedron Letters*

Received Date: 20 July 2012
Revised Date: 19 September 2012
Accepted Date: 9 October 2012

Please cite this article as: Zhou, J., Huang, L., Li, Y-Q., Du, Z-T., Synthesis of substituted 6*H*-benzo[*c*]chromenes: A palladium promoted ring closure of diazonium tetrafluoroborates, *Tetrahedron Letters* (2012), doi: http://dx.doi.org/10.1016/j.tetlet.2012.10.038

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis of substituted 6*H*-benzo[*c*]chromenes: A palladium promoted ring closure of diazonium tetrafluoroborates

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
6*H*-benzo[*c*]chromene
palladium-catalysed
diazonium salt

ABSTRACT

A highly efficient palladium-catalysed phenyl diazonium tetrafluoroborate participation of C-H activation ring closure protocol has been developed. A series of 6*H*-benzo[*c*]chromenes have been synthesized by intramolecular cyclization of ortho diazonium salts tetrafluoroborate of benzyloxyphenyl (Method A) or phenoxymethyl phenyl diazonium (Method B). The transformation allows the synthesis of 6*H*-benzo[*c*]chromenes with a wide variety of functional groups and substitution patterns from simple and easily accessible precursors.

Development of drug-like heterocyclic compounds from simple and facile substrates is one of the emerging areas in modern synthetic chemistry. The benzochromene ring is an important heteroaromatic system found in many natural products and bioactive molecules[1]. Especially, 6*H*-benzo[*c*]chromene is a structural scaffold which can be found in natural product such as cannabinol[2], whose analogues show antiemetic[3], analgesic[4], and anticonvulsant[5] properties and leading compound such as selective progesterone receptor modulators (SPRMs)[6] (Figure 1).

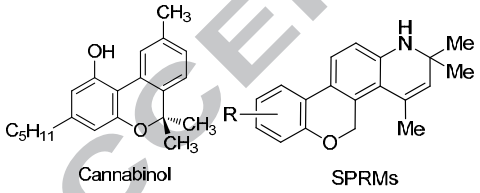
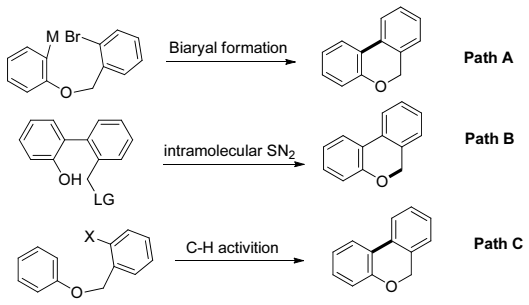


Figure 1. Typical compounds of 6H-benzo[*c*]chromenes

Generally, the classical methods for the synthesis of 6*H*-benzo[*c*]chromenes can be divided two different methodologies (Scheme 1). One is an intramolecular biaryal formation of phenylbenzyl ether such as Suzuki-Miyaura[7], Negishi, Kumada-Corriu and Hiyama coupling [8](Scheme 1, Path A). The other is an intramolecular SN_2 reaction of a preset biphenyl to construct the middle ring [9](Scheme 1, Path B). However, these approaches usually present significant limitations in terms of substituents that can be introduced, the substitution pattern, or regioselectivety. The novel C-H functionalization of phenylbenzyl ether strategies have been described in recent years[10] where simple arenes are used in place of the organometallic component. As a matter of fact, the functionalization of aromatic C-H bonds have become one of the most efficient strategies in the synthesis of the universal existence of aromatic functionalities in nature and other specific structures [11](Scheme 1, Path C). However, a general, regioselective approach to generate 6*H*-benzo[*c*]chromenes with a wide functional group tolerance from readily available precursors is still lacking. More specifically, access to highly halo substituted 6*H*-benzo[*c*]chromenes is particularly limited.

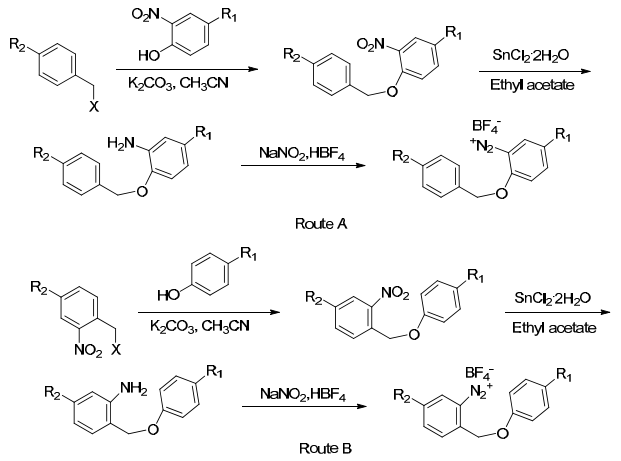
Our research group has been devoted to searching new heterocyclic structures which serve as potential bioactive compounds in agriculture[12]. Recently we disclosed the palladium-catalysed intramolecular coupling of diazonium salts and its application to the synthesis of dibenzofurans[12b]. On the basis of these results, we envisioned taking advantage of a palladium-catalysed diazonium salts as a new means to prepare heterocyclic structures which would overcome the lack of classical methods. Herein, we describe a convenient and efficient procedure for the synthesis of highly substituted 6*H*-benzo[*c*]chromenes by Pd-catalysed C-H activation of diazonium salts in moderate to good yields.



Scheme 1. Pathways of synthesis of 6H-benzo[*c*]chromene

As shown in Scheme 2, a variety of diazonium substrates were prepared according to literature, through the etherification of

corresponding phenols and benzyl halide [13a,b], reduction by $SnCl_2$ dihydrate and diazonation in the presence of sodium nitrite and HBF_4[13c] in good overall yields. Different substituents on the benzyl, including alkyl and halo moieties, as well as several functional groups, are tolerated in the substrates preparations.



Scheme 2. The preparation of substrates for cyclization in Method A and Method B.

With these diazonium substrates tetrafluoroborates in hand, we next tested six-membered ring formation by palladium-catalysed cyclization. In contrast to $Pd(PPh_3)_4$ and $Pd(CH_3CN)_2Cl_2$, $Pd(OAc)_2$ (Table

1, entries 4, 9-10) provided higher yields in same conditions. The choice of the base also plays a crucial role. In comparison with organic bases, the inorganic ones were more effective for the preparation of 6*H*-benzo[*c*]chromene (Table 1, entries 4-8). Our studies subsequently showed that the reaction solvent seems to be crucial to this reaction. Acetone and DMF were found to be less productive, whereas ethanol can improve the yield markedly (Table 1, entries 1-3). It is worth pointing out that when acetonitrile was used, the highest yield was obtained (Table 1, entry 4). We believe that nonproton solvents are beneficial in this process in that they can suppress the denitrification to arene. Finally, we set up the optimum reaction conditions that are acetonitrile as solvent, 5% molar ratio $Pd(OAc)_2$ as catalyst, 150% molar ratio K_2CO_3 as base at refluxing temperature (Table 1, entry 4).

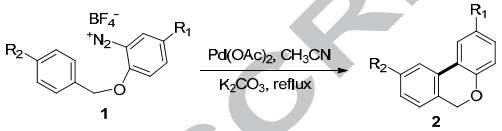
Table 1. Screening of reaction conditions for the cyclization of 2-(benzyloxy)benzenediazonium tetrafluoroborate

Entry	Catalyst	Base	Solvent	Temperature (°C)	Yield (%)[a]
1	$Pd(OAc)_2$	K_2CO_3	DMF	100	<5
2	$Pd(OAc)_2$	K_2CO_3	EtOH	reflux	58
3	$Pd(OAc)_2$	K_2CO_3	Acetone	reflux	0
4	$Pd(OAc)_2$	K_2CO_3	CH_3CN	reflux	75
5	$Pd(OAc)_2$	none	CH_3CN	reflux	30[b]
6	$Pd(OAc)_2$	Na_2CO_3	CH_3CN	reflux	45
7	$Pd(OAc)_2$	Cs_2CO_3	CH_3CN	reflux	40
8	$Pd(OAc)_2$	Et_3N	CH_3CN	reflux	<5
9	$Pd(PPh_3)_4$	K_2CO_3	CH_3CN	reflux	48
10	$Pd(CH_3CN)_2Cl_2$	K_2CO_3	CH_3CN	reflux	60

a: isolated yield. b: the reaction is slow.

Under this optimized reaction conditions, the scope of Pd-catalysed cyclization of 2-(benzyloxy)benzenediazonium tetrafluoroborate was explored for the synthesis of substituted 6*H*-benzo[*c*]chromenes. A variety of functional groups were tolerated(Table 2), including chloro (Table 2, entries 3, 7, 11) and bromo (entries 2, 8, 12). The transformation described herein allows the synthesis of corresponding 6*H*-benzo[*c*]chromenes in 68-83% yields. Moreover, the presence of either electron-withdrawing or electron-donating groups on the benzyl does not hinder the reaction (entries 13-14). Access to halo 6*H*-benzo[*c*]chromenes is particularly noteworthy as synthetic routes to such compounds are rare, which can be functionalized to other moieties or subjected by cross coupling reaction. Thus, all the products in our reactions listed in Table 2 were easily characterized on the basis of physical and spectral data and also by comparison with authentic samples. The ORTEP of **2h** was shown in Figure 2.

Table 2. $Pd(OAc)_2$ catalysed cyclization 2-(benzyloxy)benzenediazonium tetrafluoroborate (Method A)



entry	1, 2	2-phenoxybenzenediazonium tetrafluoroborate	Isolated yield
1	a	R_1 =H, R_2=H	75
2	b	R_1 =H, R_2=Br	68
3	c	R_1 =H, R_2=Cl	70
4	d	R_1 =H, R_2=CH_3	76
5	e	R_1=CH_3, R_2=H	75
6	f	R_1=CH_3, R_2= CH_3	80
7	g	R_1=CH_3, R_2= Cl	72
8	h	R_1=CH_3, R_2= Br	71
9	i	R_1 =*t*-Bu, R_2=H	78
10	j	R_1 =*t*-Bu, R_2= CH_3	83
11	k	R_1 =*t*-Bu, R_2= Cl	76
12	l	R_1 =*t*-Bu, R_3= Br	72
13	m	R_1 =H, R_2=OMe	48
14	n	R_1 =COOEt, R_2=H	83

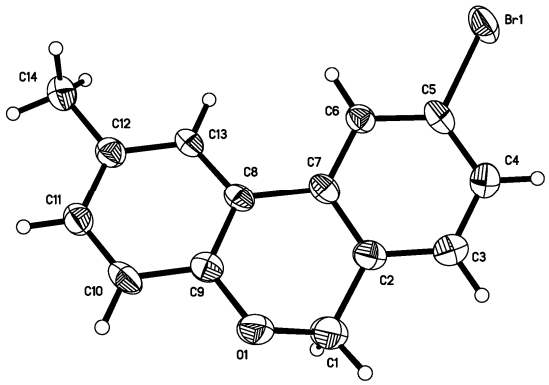
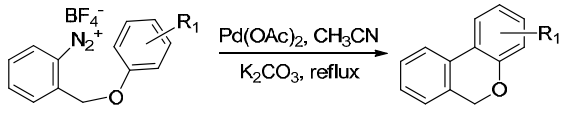


Figure 2. OPTEP drawing of the crystal structure of 2h

The alternative pathway to 6*H*-benzo[*c*]chromenes was also studied (Scheme 2, Method B). The diazonium moieties were changed to another phenyl rings (Scheme 1, Method B), thus an extension of the synthetic approach to 6*H*-benzo[*c*]chromenes can also be furnished. As the results in Table 3 indicate, seven 6*H*-benzo[*c*]chromenes can be obtained smoothly in all cases in 50-68% yield. The transformation also allowed the synthesis of 6*H*-benzo[*c*]chromenes bearing different halogen sources in good yields (Method B).

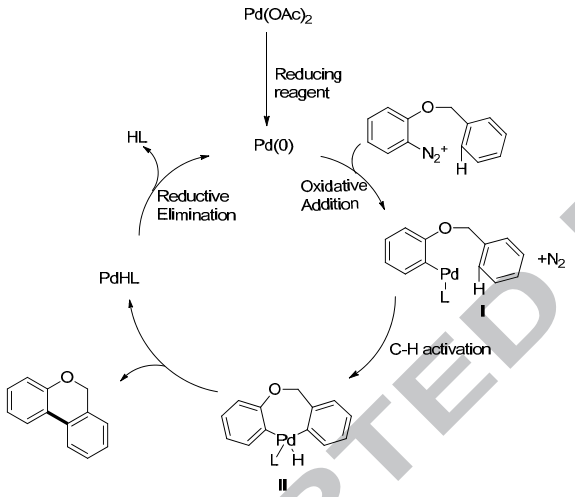
Table 3. Pd(OAc)2 catalysed cyclization phenoxymethyl phenyl diazonium tetrafluoroborate (Method B)



3 **4**

entry	3, 4	phenoxymethyl diazonium tetrafluoroborate	phenyl	Isolated yield
1	a	R_1=H		65
2	b	R_1 =4-F		52
3	c	R_1 =4-Cl		50
4	d	R_1 =4-Br		68
5	e	R_1 =4-CH_3		58
6	f	R_1=2-CH_3		57

A plausible mechanism of the intramolecular cyclization is proposed in Scheme 3. The beneficial effect of diazonium salt led us to consider its mechanism as Palladium-catalysed tandem denitrification/C-H Activation[12b, 14]. First, Pd (II) was firstly reduced to Pd (0) by reducing reagent. Then an oxidative addition to the diazonium salt gave intermediate **I** and evolved a nitrogen. Finally, A C-H insertion of Pd formed seven-membered intermediate **II**, which reductive eliminate to give dibenzofuran and regenerate Pd (0). Last, but not least, it should be noted that the large volume N_2 evolution when this method is used on large scale.



In conclusion, an extremely efficient Pd-catalysed protocol for the synthesis of 6*H*-benzo[*c*]chromenes from 2-phenoxybenzenediazonium or phenoxymethyl phenyl diazonium tetrafluoroborate has been developed. This transformation is distinguished by its mild conditions, allowing the tolerance of a wide variety of functional groups, especially halogen functional groups tolerance. Further work is in progress to broaden the scope of this methodology.

Acknowledgments

Financial support from the Fundamental Research Funds for the Central Universities in NWSUAF (No. QN2009048) and the National Natural Science Foundation of China (20802058) is greatly appreciated.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi 10.1016/j.tetlet.2012.10.038.

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15. *General procedure for the preparation of 6H-benzo[c]chromenes from of ortho diazonium salts using Pd(OAc)$_2$*: At argon, a suspension of ortho diazonium salts corressponding (5 mmol) in acetonitrile (20 ml), catalytic $Pd(OAc)_2$ (56mg, 0.25mmol) and (1.0 g, 7.5mmol) K_2CO_3 was refluxed for 2-6 hours. The mixtures were evaporated under vacuum and the residue was purified by column chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate to give 6*H*-benzo[*c*]chromenes.
16. Selected spectrum data of **2h**: ^{1}H NMR (500 Hz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.50 (s, 1 H), 7.41 (d, 1 H, *J* = 8 Hz), 7.12 (d, 1 H, *J* = 8 Hz), 7.02(d, 1 H, *J* = 8 Hz), 6.95 (d, 1 H, *J* = 8 Hz), 5.04 (s, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.7, 132.4, 131.6, 130.9, 130.3, 130.2, 126.3, 125.0, 123.8, 122.4, 121.4, 117.2, 68.0, 21.0 ppm.

Graphical Abstract

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Synthesis of Substituted 6*H*-benzo[*c*]chromenes: A Palladium promoted Ring closure of diazonium tetrafluoroborates

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