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Facile Synthesis of Polycyclic Fluorene Derivatives *via* a Palladium-Catalyzed Coupling, Propargyl-Allenyl Isomerization and Schmittel Cyclization Sequence

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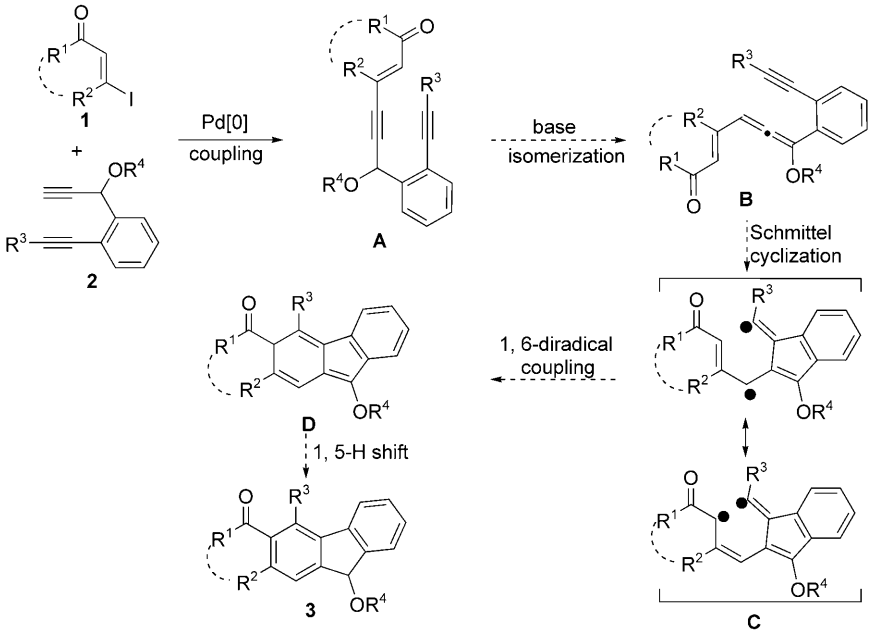
Abstract: A stepwise process involving Sonogashira coupling, propargyl-allenyl isomerization and Schmittel cyclization has been realized, leading to an efficient synthesis of polycyclic fluorene derivatives from readily available starting materials. The reaction features the formation of three new carbon-carbon bonds to construct the benzene unit together with an efficient assembly of three or four rings in a single operative step.

Keywords: allenes; fluorenes; Schmittel cyclization; sequential reactions

The synthesis of various carbocycles *via* efficient formation of carbon-carbon bonds is a highly desired activity in organic synthesis.[1] Sequential reactions that often feature formation of several bonds and stereocenters in a single step, have received great attention because they address fundamental principles of synthetic efficiency and reaction processing.[1,2] With delicate design, these reactions often allow an efficient and straightforward access to novel and complex carbocycles and heterocycles from simple or readily accessible starting materials, and have been widely employed for the synthesis of the core skeleton of many important natural products.[3]

Müller et al. pioneered the Sonogashira coupling-isomerization reactions for the synthesis of a variety of useful compounds including chalcones, pyrazolines, pyrroles, fluorescent spirocycles, and some other pharmaceutically interesting heterocycles.[4] Starting from electron-deficient vinyl iodides and propargyl ethers, we previously established an interesting palladium-catalyzed sequential reaction wherein the *in situ* generated vinylallene intermediate would undergo a Diels–Alder reaction under mild conditions, providing an efficient synthesis of structurally complex polycycles with 2,3-dihydrofuran units[5a] and structurally diverse fused dihydroisobenzofuran derivatives.[5b] Furthermore, our continuing study led us to an unexpected observation that the involved vinylallene intermediates can also be trapped by an intramolecular Alder-ene reaction to produce some structurally interesting 2,3-dihydrofurans, making these reactions an attractive diversity-oriented approach to access a variety of useful skeletons.[5c]

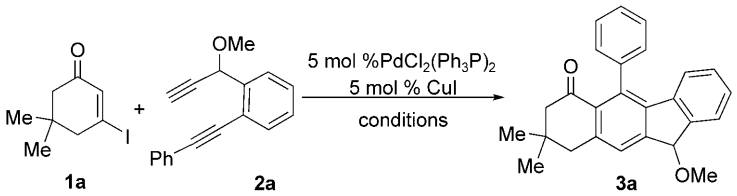
As part of our continuing efforts in this chemistry, herein we envisioned a novel sequence of palladium-catalyzed coupling, propargyl-allenyl isomerization and Schmittel cyclization.[6] The enyne-allene intermediate **B**, which is expected to be generated *in situ* from the palladium-catalyzed coupling reaction of electron-deficient vinyl iodide **1** with 1-(2-alkynylphenyl)propargyl ether **2** followed by propargyl-allenyl isomerization, may preferentially cyclize to produce a benzofulvene diradical **C** *via* Schmittel cyclization;[6,7] then an intramolecular 1,6-diradical coupling reaction and 1,5-H shift may proceed to furnish the fused cyclic compound **3** (Scheme 1). Appealingly, with this strategy three new carbon-carbon bonds can be formed to construct the benzene ring while three or four rings could be efficiently assembled in a single stroke, resulting in an attractive synthesis of fluorene derivatives, which are of considerable interest[8] since fluorenes are a useful class of compounds with high utility as building blocks for advanced materials with unique electrical and optical properties[9] and the fluorene unit frequently shows up in bioactive molecules.[10] In this paper we wish to report our results on this sequential reaction.



Scheme 1. Reaction design for a tandem palladium-catalyzed coupling, propargyl-allenyl isomerization, Schmittel cyclization sequence.

We began our investigations into the feasibility of this cascade process using 3-iodo-5,5-dimethylcyclohex-2-enone (**1a**) and 1-[2-(2-phenylethynyl)phenyl]-prop-2-ynyl methyl ether (**2a**), treatment of which with a catalytic amount of $PdCl_2(Ph_3P)_2$ and CuI in toluene and Et_3N at 100 °C for 5 h successfully led to the desired product **3a** in 73% yield (Table 1, entry 1). When the reaction was performed at 60 °C, the yield was improved to 84% (entry 2). The reaction proceeded as well at room temperature although a prolonged reaction time was needed, affording **3a** in 60% yield (entry 4). Further experiments demonstrated that the reaction conducted in solvents such as THF, MeCN and DMF, furnished **3a** in inferior yields (entries 5–7). Therefore, we established the proposed sequential reaction conducted in toluene and Et_3N at 60 °C under the catalysis of 5 mol% $PdCl_2(Ph_3P)_2$ and 5 mol% CuI.

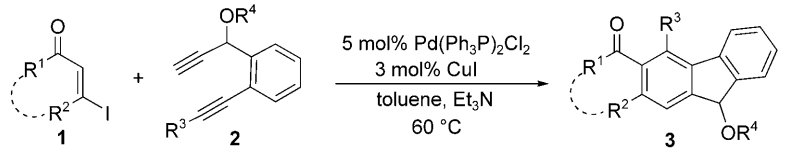
Table 1. Solvent and temperature effects on the sequential reaction.[a]

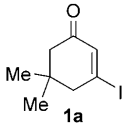
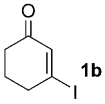
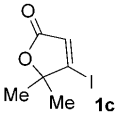
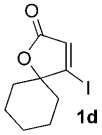
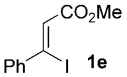


Entry	Solvent	Temperature [°C]	Time [h]	Yield [%][b]
1	Toluene	100	5	73
2	Toluene	80	7	76
3	Toluene	60	7	84
4	Toluene	room tempertaure	24	60
5	THF	60	6	61
6	MeCN	60	5	67
7	DMF	60	3	53[c]

[a] Reactions were carried out using **1a** (0.2 mmol), **2a** (0.24 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), and CuI (5 mol%) in 1.8 mL of solvent and 0.6 mL of Et_3N.
[b] Isolated yields.
[c] Contaminated with small amount of unknown by-products.

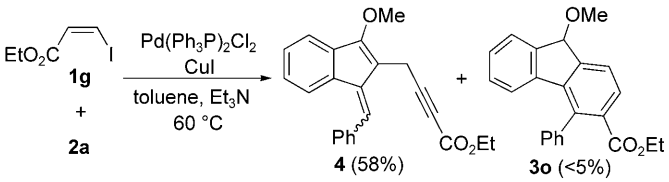
Table 2. Sequential reaction of electron-deficient vinyl iodides **1** with 1-(2-alkynylphenyl)propargyl ethers **2**.[a]



Entry	1	2		Time [h]	Product 3	Yield [%][b]
		R^3	R^4			
1	 **1a**	Ph	Me (**2a**)	7	**3a**	84
2	**1a**	*p*-EtC_6H_4	Me (**2b**)	7	**3b**	87
3	**1a**	*p*-ClC_6H_4	Me(**2c**)	6	**3c**	75
4	**1a**	Ph	Bn (**2d**)	7	**3d**	84
5	**1a**	*p*-ClC_6H_4	Bn (**2e**)	6.5	**3e**	80
6	**1a**	Ph	Allyl (**2f**)	6.5	**3f**	85
7	 **1b**	Ph	Me (**2a**)	7	**3g**	83
8	**1b**	Ph	Hept-2-ynyl (**2g**)	5	**3h**	74
9	**1b**	*n*-C_6H_{13}	Me (**2h**)	9	–[c]	–
10	 **1c**	Ph	Me (**2a**)	6	**3i**	73
11	**1c**	*p*-EtC_6H_4	Me (**2b**)	7	**3j**	70
12	**1c**	*p*-ClC_6H_4	Me (**2c**)	6	**3k**	71
13	 **1d**	*p*-EtC_6H_4	Me (**2b**)	4.5	**3l**	88
14	 **1e**	Ph	Me (**2a**)	7	**3m**	41
15	**1e**	*p*-EtC_6H_4	Me (**2b**)	6	**3n**	47

[a] Reactions were carried out using **1** (0.2 mmol), **2** (0.24 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), and CuI (5 mol%) in 1.8 mL of toluene and 0.6 mL of Et_3N at 60 °C.
[b] Isolated yields.
[c] Small amount of unidentified mixture was obtained.

With the optimal conditions in hand, we next examined the reaction scope. Typical results are summarized in Table 2. As for 1-(2-alkynylphenyl) propargyl ethers **2** wherein R^3 is an aromatic group such as phenyl, *p*-ethylphenyl and *p*-chlorophenyl group, the reactions with 3-iodocyclohex-2-enone **1a** or **1b** proceeded smoothly under the established conditions, delivering the fluorenes **3** in good yields (Table 2, entries 1–8). However, when R^3 is an alkyl group, for example, **2h**, the reaction did not give the expected product but a small amount of an unidentified mixture (entry 9), probably due to the dominating occurrence of the Myers–Saito cyclization which complicated the reaction.[11] The substituents R^4 seem to have no such significant effect on this reaction although it was observed that the yields differed to some extent with this factor. R^4 can be Me or Bn, and interestingly allyl or propargyl groups were also well tolerated. For examples, when **2f** and **2g** were employed to react with 3-iodocyclohex-2-enone, the corresponding products **3f** and **3h** were obtained in 85% and 74% yields, respectively. Here it is worth noting that in either case we did not observe the formation of any Diels–Alder cycloadduct of the vinylallene intermediate with the alkene or alkyne moiety of R^4,[5a,b] indicating that the Schmittel cyclization of the presumed enyne-allene intermediate such as **B** (Scheme 1) proceeds preferentially rather than the Diels–Alder reaction. In



Scheme 2.

addition to 3-iodocyclohex-2-enone **1a** and **1b**, the reaction was also applicable to other electron-deficient vinyl iodides such as 3-iodobutenolides **1c** and **1d**, producing the corresponding products in good yields (entries 10–13). When (*Z*)-methyl 3-iodo-3-phenylacrylate (**1e**) was employed, the desired products **3m** and **3n** were also obtained, albeit in lower yields (entries 14 and 15). However, when we carried out the reaction of (*Z*)-ethyl 3-iodoacrylate (**1g**) and **2a** under the established conditions, only a small amount of fluorene compound **3o** was isolated with the indene **4** as the main product (Scheme 2). Compound **4** may result from other transformations of the Schmittel-cyclization diradical intermediate of the involved enyne-allene intermediate.[6c,12] All of the products were characterized by spectroscopic methods, and **3i** was further confirmed by X-ray crystallography (Figure 1).[13]

Furthermore, to expand the scope of this reaction, we also investigated a range of electron-deficient aromatic halides. We found that the reaction is applicable to those with moderate electron-withdrawing groups such as 4-iodobenzonitrile (**5b**), 1-(4-iodophenyl)ethanone (**5c**) and 4-bromobenzaldehyde (**5d**), affording benzofluorenes **6b–e** in moderate to good yields (Table 3, entries 2–5). However, as for 1-iodo-4-nitrobenzene (**5e**) in which a strong electron-withdrawing group is incorporated, the reaction failed to give any identifiable product (entry 6), indicating that the nature of the electron-withdrawing group on the aromatic ring may play a significant role in this reaction. In addition, as an example for comparison we also conducted the reaction of 1-iodobenzene (**5a**) and **2a**, which exclusively gave the coupling product **6a** in a yield of up to 95% (entry 1). The benzofluorene compound was not formed in this case mainly due to the

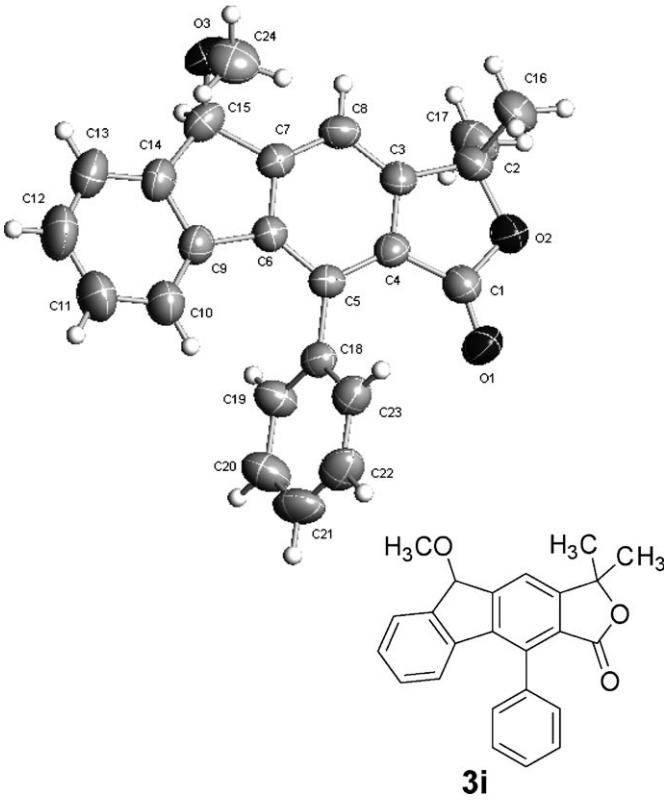
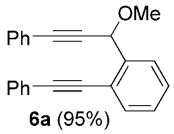
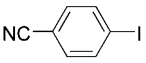
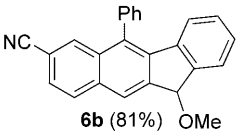
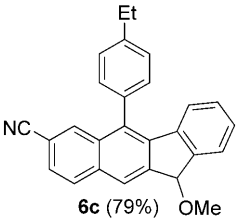
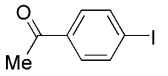
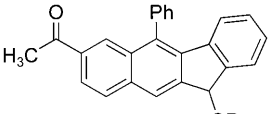
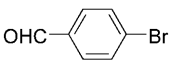
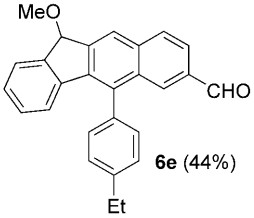
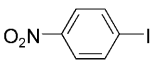


Figure 1. ORTEP representation of **3i**.

Table 3. Sequential reaction of aromatic halides **5** and 1-(2-alkynylphenyl)propargyl ethers **2**.[a]

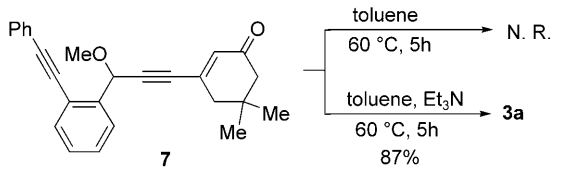
Entry	5	2	6 (Yield[b])
1	 **5a**	**2a**	 **6a** (95%)
2	 **5b**	**2a**	 **6b** (81%)
3	**5b**	**2b**	 **6c** (79%)
4	 **5c**	**2d**	 **6d** (51%)
5	 **5d**	**2b**	 **6e** (44%)
6	 **5e**	**2a**	–

[a] Reactions were carried out using **1** (0.2 mmol), **2** (0.24 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), and CuI (5 mol%) in 1.8 mL of toluene and 0.6 mL of Et_3N at 100 °C.

[b] Isolated yields.

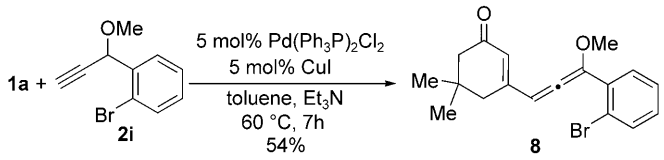
fact that the absence of an electron-withdrawing group makes the propargyl-allenyl isomerization of **6a** reluctant to produce an allene species, which is crucial for the subsequent transformation.

The control experiments also revealed that the *in situ* generation of an allene intermediate was crucial in the reaction. It was found that no reaction occurred by direct heating of the coupling product **7** in toluene, whereas the addition of amine base, which may facilitate a propargyl-allenyl isomerization process, successfully led to the formation of **3a** (Scheme 3). Indeed, after extensive study on the reaction of **1a** with a variety of 1-arylpropargyl methyl ethers, quite



Scheme 3.

recently we for the first time successfully confirmed and characterized an isolable vinylallene intermediate **8**, which provided strong and direct evidence for the proposed reaction pathway (Scheme 4).[14]



Scheme 4. Confirmation of an isolable vinylallene intermediate **8**.

In conclusion, we have developed a convenient sequential palladium-catalyzed coupling, propargyl-allenyl isomerization and Schmittel cyclization reaction, leading to a facile and efficient synthesis of polycyclic fluorene derivatives from a variety of electron-deficient vinyl iodides or aromatic halides with 1-(2-alkynylphenyl)propargyl ethers. In respect to the easy availabilty of the starting materials, simple manipulation, mild conditions and high efficiency, this reaction will be synthetically useful in organic chemistry. Further studies on the scope of this reaction are currently underway in our laboratory.

Experimental Section

Typical Procedure

An oven-dried Schlenk tube containing a Teflon-coated stir bar was charged with $PdCl_2(PPh_3)_2$ (8.0 mg, 5 mol%), CuI (2.0 mg, 5 mol%). The Schlenk tube was sealed and then evacuated and backfilled with N_2 (3 cycles). A solution of **1a** (50 mg, 0.2 mmol) and **2a** (59 mg, 0.24 mmol) in 1.8 mL of toluene and 0.6 mL of Et_3N was subsequently injected to the Schlenk tube. The reaction mixture was stirred at 60 °C for 7 h. After removal of the solvent under vacuum, the residues were purified with flash chromatography (silica/petroleum ether:ethyl acetate 8:1) to afford **3a**; yield 62 mg (84%).

Acknowledgements

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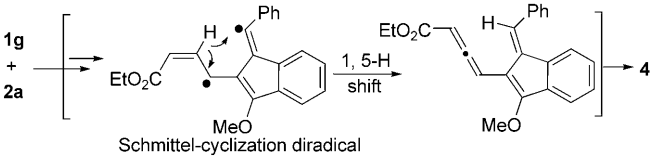

[13] X-ray crystal data for **3i**: $C_{24}H_{20}O_3$; MW = 356.40; orthorhombic, space group *P2(1)2(1)2(1)*; $a = 9.3902(8)$, $b = 10.6935(9)$, $c = 18.8166(17)$ Å; $\alpha = 90.00$, $\beta = 90.00$, $\gamma = 90.00$, $V = 1889.5(3)$ Å^3, $T = 293$ (2) K, $Z = 16$, $\rho_{calcd} = 1.253$ Mg/m^3, $\mu = 0.082$ mm^{-1}, $\lambda = 0.71073$ Å.; F(000) 752, independent reflections ($R_{int} = 0.0556$), 11471 reflections collected; refinement method, full-matrix least-squares refinement on F_2; goodness-of-fit on $F_2 = 0.858$; final R indices [$I > 2\sigma(I)$] $R_1 = 0.0371$, $wR_2 = 0.0744$. CCDC 745875 contains the supplementary crystallographic data for compound **3i**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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