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FULL PAPER

TfOH catalyzed synthesis of 9-arylfluorenes via tandem reaction under warm and efficient conditions

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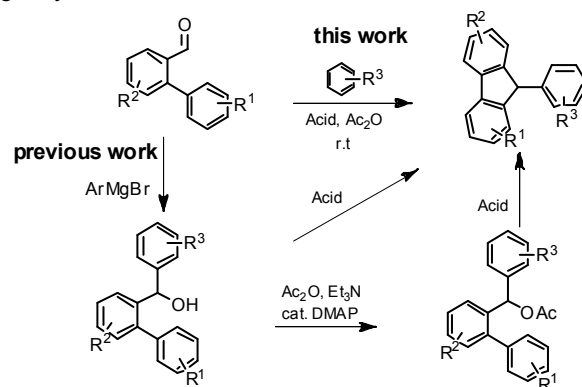
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A tandem ring-closing reaction was developed for the synthesis of 9-arylfluorenes and derivatives. The reaction is metal-free, straightforward and efficient under warm conditions. Higher than 99% yield is obtained.

9-arylfluorenes attract many researchers' attention for their promising potential applications in materials, including blue fluorescent organic light emitting materials, thin film transistors, photovoltaic cells, etc.¹ On the other hand, Friedel Crafts reaction plays an important role in C-C bonds building, especially the tandem Friedel Crafts reaction, which economically constructs two C-C bonds in one step. To date, many extramolecular tandem reactions with aromatic aldehydes have been described by researchers.² However, to our best knowledge, intramolecular tandem reactions of aromatic aldehydes are rarely reported.³ Our groups have concentrated on the research of tandem reaction for its advantages in building complicated compounds. Recently, our group report an one-pot three-component reaction for the synthesis of benzofuro[2,3-c]pyridines.⁴ Herein, an environmentally friendly and efficient Tandem ring-closing Friedel Crafts reaction is developed for the synthesis of 9-arylfluorenes.

The synthetic methods of 9-arylfluorenes were widely researched. In 2011, Chen reported a reaction of fluorenes and haloarenes generates 9-arylfluorenes via palladium-catalyzed arylation at 130 °C.⁵ Recently, Teng' group synthesize 9-arylfluorenes from triarylcarbinols in the presence of p-toluenesulfonic acid (TsOH), in benzene.⁶ In 2012, Das and his co-workers built a tandem ring-closing sequence catalyzed by a Pd-Sn heterobimetallic catalyst with AgPF₆ as additive,³ which is a novel strategy about intramolecular tandem reactions. But, according to this article, biaryl alcohols have to be synthesized firstly from 2-arylbenzaldehydes to further prepare 9-arylfluorenes. Similarly, Li' and Sarkar' group developed a general and efficient synthesis of 9-arylfluorenes via Grignard addition and Friedel Craft cyclization reactions from 2-arylbenzaldehydes (Scheme 1).⁷ However, the strategy is not economic and convenient enough. In summary, an environmentally friendly and efficient method is still desired for the synthesis of 9-arylfluorenes. In this article, we report a method to prepare 9-arylfluorenes from 2-arylbenzaldehydes in the catalyst system of TfOH and acetic anhydride via tandem Friedel Crafts reactions at room temperature in acceptable to

great yields.



Scheme 1 Synthetic approaches for 9-arylfluorenes

First, we attempted the tandem reaction of 2-phenylbenzaldehyde with arene. Encouragingly, 2-phenylbenzaldehyde transformed into 9-mesityl-9H-fluorene at 80 °C in good yield (Table 1, entry 1), but mesitylene was necessarily solvent. Considering the acetal and acylal being active substrates,⁸ 1,3-propanediol was added to the reaction, but no product was detected at room temperature (Table 1, entry 2). However, to our delight, after adding two times amount of acetic anhydride, expected product was obtained in excellent yield in DCE at room temperature (Table 1, entry 3). If less acetic anhydride was added to the reaction, the yield decreased slightly to 87% (Table 1, entry 4). Notably, no product was gained, when no acetic anhydride was added at room temperature (Table 1, entry 5).

Further, in pursuit of the catalytic version, we investigated the tandem alkylation in the presence of various acids (Table 1, entries 6-10). H₂SO₄ and BF₃·Et₂O could also catalyze the reaction well (entries 6 and 7). Trace of benzylidene diacetate was detected after 1.5 h in the both reactions and, finally, good yields were obtained in 83% and 90%, respectively. CF₃COOH, p-toluenesulfonic acid and camphorsulfonic acid (CSA) had no catalytic effect (entries 7-9). Significantly, besides in DCE, the reaction may proceed in other non-polar solvents (Table 1, entries 11-13). Almost identical result was obtained in DCM (entry 11). And in nitromethane and n-hexane, good yields were obtained (entries 12 and 13). However, in polar solvent: EtOH, THF and

1,4-dioxane, the reaction couldn't proceed (entries 14-16).

Table 1 Optimization of reaction conditions^a



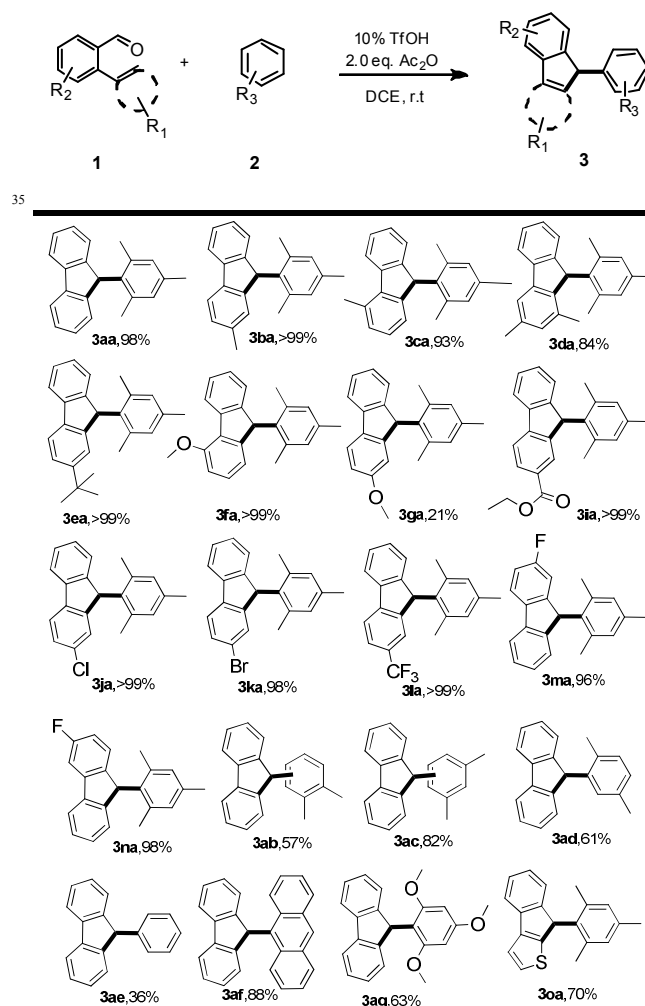
Entry	Catalyst	Solvent	Time /h	Yield (%) ^b
1 ^c	TfOH	mesitylene	24	75
2 ^d	TfOH	DCE	24	ND ^e
3	TfOH	DCE	0.5	98
4 ^f	TfOH	DCE	24	87
5 ^g	TfOH	DCE	24	ND
6	H ₂ SO ₄	DCE	22	83
7	BF ₃ · Et ₂ O	DCE	22	90
8	CF ₃ COOH	DCE	24	ND
9	TsOH	DCE	24	ND
10	CSA	DCE	24	ND
11	TfOH	DCM	1	96
12	TfOH	n-hexane	1.5	79
13	TfOH	nitromethane	1.5	87
14	TfOH	EtOH	24	ND
15	TfOH	THF	24	ND
16	TfOH	1, 4-dioxane	24	ND

^a Reactions were conducted with 0.5 mmol of **1a**, 2.5 mmol of **2a** and 1.0 mmol acetic anhydride in 5 ml solvent at room temperature. ^b Isolated yields. ^c No acetic anhydride, mesitylene as solvent, at 80 °C. ^d No acetic anhydride, 1.0 mmol 1,3-propanediol. ^e No product was detected. ^f 0.5 mmol acetic anhydride. ^g No acetic anhydride.

The activity of various groups substituted 2-phenyl benzaldehydes were widely investigated under the optimal conditions (Table 1, entry 3). Methyl group substituted 2-phenyl benzaldehydes may transform into products in almost quantitative yields (Table 2, **3ba-3da**). **3ba** and **3ca** were obtained in 93% and >99% yields, respectively. The substrate bearing dimethyl group got a lower yield (84%) due to steric hindrance (**3da**). Tertiary butyl substituted substrate also proceeded well to afford **3ea** in >99% yield. Moreover, methoxy group substituted substrates got different yields. **3fa** was obtained in >99% yield but 9-mesityl-2-methoxy-9H-fluorene in 21% yield (**3ga**). The phenomenon is strange and interesting. We try to figure it out. In contrast, 2-arylbenzaldehydes bearing electron-withdrawing substituent transformed into products effectively (**3ia-3la**). Acetoxyl, chlorine, bromine and even trifluoromethyl substituted 2-arylbenzaldehydes were transformed almost quantitatively into desired products. Notably, to the substrates of formyl group's aromatic rings bearing electron-withdrawing substituents, great yields were obtained (**3ma** and **3na**). We also investigated the scope of arenes (**3ab-3ag**). Good to great yields were obtained with electron-rich arenes (**3ab-3ad**, **3af**, **3ag**), while electron-deficient benzene couldn't proceed smoothly. The thing to note

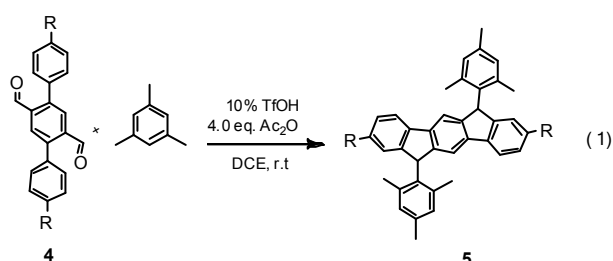
here is that target products from dimethyl-substituted arenes have regioselectivity and stereoselectivity (**3ab-3ad**). Unfortunately, when more electron-deficient chlorobenzene or nitrobenzene was employed, no product was gained. Remarkably, 2-(thiophen-3-yl)benzaldehyde cyclized into the corresponding indeno[2,1-b]thiophene in good yield under optimal conditions (**3oa**).

Table 2 Substrate scope of tandem Friedel Craft reaction^a

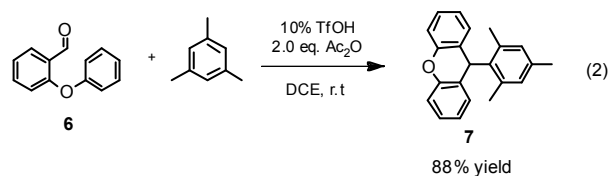


^a Reactions were conducted with 0.5 mmol of **1** and 2.5 mmol of **2** under the optimal conditions unless otherwise stated and isolated yields are shown.⁹ Regioselectivity: **3ab** (88:12); **3ac** (62:38); Stereoselectivity: **3ad** (63:37). These ratios were determined by ¹H NMR. For details about the rotamers of **3ad**, see: ref.⁵

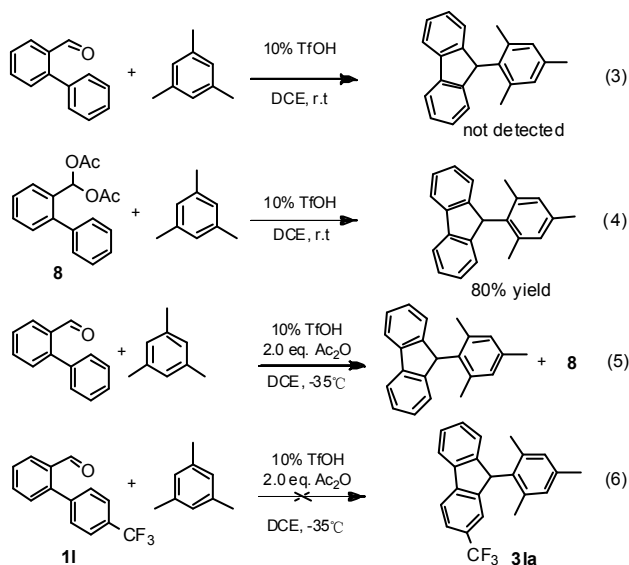
Furthermore, both potentially reactive C=O bonds in substrates could convert smoothly into indeno[1,2-b]fluorene derivatives (eq 1). Such products present more advantages than monofunctional products as blue fluorescent organic light emitting materials. More importantly, indenofluorene derivatives are potential and vital candidates as organic semiconductors for use in thin-film transistors and light-emitting diodes.¹⁰ The methodology could also be applied to 2-phenoxybenzaldehyde to afford xanthene (**7**), which is a type of important intermediate of drugs and dyes (eq 2).



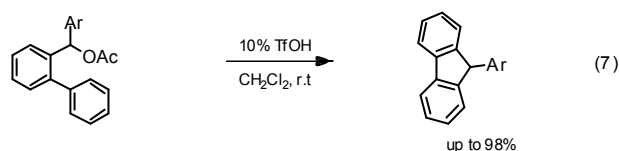
5a R=CF₃ (81% yield);
5b R=C(CH₃)₃ (79% yield).



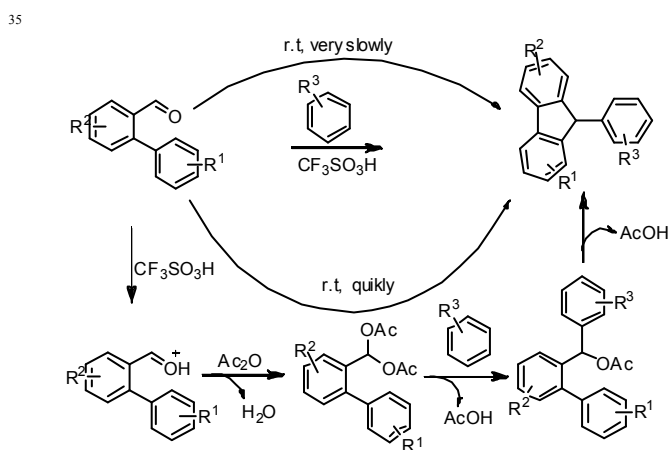
According to our investigations, acetic anhydride has a crucial role in the reaction. Further investigation was conducted in the purpose of figuring out the mechanism of the reaction (Scheme 2). Firstly, 4 Å molecular sieve was added instead of acetic anhydride (eq 3) and no product was obtained, which indicated acetic anhydride is not only as water absorbent. Notably, when the acylal from 2-benzaldehyde was treated with mesitylene in the catalysis of TfOH solely, the target compound could be synthesized successfully in 80% yield (eq 4). However, the reaction proceeds so fast that the ester intermediate can't be obtained even though at minus 35 °C with target product and the acylal **8** being detected (eq 5) while no reaction with **11** occurred (eq 6). We take advantage of previous research (eq 7)^{7(a)} and a plausible mechanism is proposed (Scheme 3). With TfOH as catalyst, acetic anhydride and the benzaldehyde afford acylal via condensation reaction. Subsequently, arene attacks the acylal and lead to the formation of corresponding biaryl alcohol ester. Finally, electrophilic substitution gives 9-arylfuorene.



Scheme 2 Controlled experiments



In conclusion, we have developed a warm and efficient tandem Friedel Craft reaction of a variety of 2-arylbenzaldehydes with arenes to give 9-arylfuorenes and indeno[1,2-b]fluorene derivatives in the catalyst system of TfOH and acetic anhydride. The corresponding products are obtained in good to almost quantitative yields when various 2-arylbenzaldehyde bearing an electron-withdrawing and electron-donating substituent are treated with electron-rich arenes. The strategy can also be applied to the synthesis of hetero indeno core and xanthene in good yields. Studies to elucidate the detailed mechanism and synthetic applications of this efficient and practical tandem reaction are under way in our laboratory.



Scheme 3 A plausible mechanism

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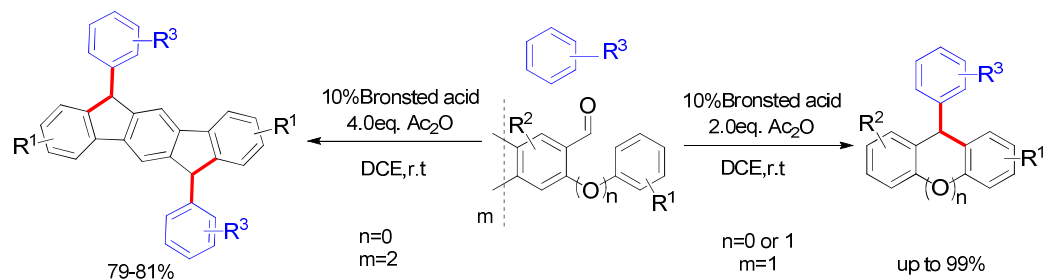
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TfOH catalyzed synthesis of 9-arylflorenes via tandem reaction under warm and efficient conditions

Graphical abstract



A straightforward and efficient protocol to synthesize 9-arylflorenes and derivatives has been successfully achieved. The tandem ring-closing reaction can reach higher than 99% yield by using TfOH and Ac₂O as catalyst system, DCE as solvent, at room temperature. Moreover, a wide range of substrates including 2-(thiophen-3-yl)benzaldehyde, difunctional dicarbaldehyde and 2-phenoxybenzaldehyde can fit with this system as well.