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The first method for C-devinylation of aromatic systems ☆

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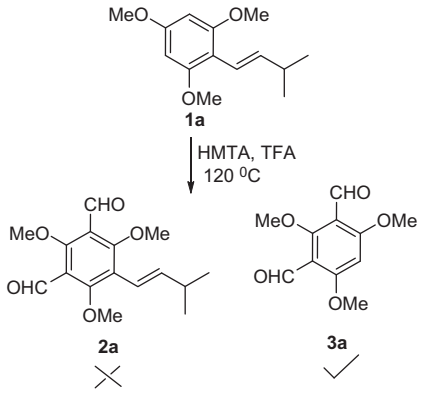
ABSTRACT

This Letter describes the method for C-devinylation of aromatic systems for the first time. Vinylbenzenes on refluxing with trifluoroacetic acid produced corresponding devinylated products in excellent yields. Furthermore, 2,4,6-trimethoxy vinylbenzenes on treatment with hexamethylene tetraamine and trifluoroacetic acid exclusively produced 1,3-diformyl 2,4,6-trimethoxy benzene via tandem devinylation and diformylation reactions. A variety of aliphatic vinyl groups can be utilized but the reaction is limited to 1,3,5-trimethoxybenzene.

Development of facile methods for the removal or deprotection of functional groups from organic molecules is immensely important in organic chemistry and biological systems.[1] Like allyl functionality, vinyl group is also used in organic synthesis as protecting group[2–4] and is widely present among natural products.[5] The vinyl group can be introduced on aromatic ring system using approaches such as formylation followed by Wittig reaction[6] and via Friedel–Craft acylation followed by reduction and dehydration.[7] However no method is available for the removal of vinyl moiety from aromatic system, although there exist a few reports on devinylation of other systems such as pyrroles,[8] lactams,[9,3] imidazoles,[2] benzimidazoles,[4] pyrazoles,[10] and porphyrins.[11] All these reported devinylation strategies are for N-devinylation and involves oxidative or hydrolytic cleavage; however no report exists for C-devinylation. In continuation of our recent reports on deprotection strategies,[12,9] herein we report devinylation of vinylbenzenes under Duff reaction conditions (Scheme 1).

Duff reaction is a formylation reaction discovered by James Cooper Duff in 1920,[13,14] and is widely used in organic chemistry for the introduction of formyl functionalities on a variety of aromatic substrates using hexamine/TFA reagent.[13,15] The reaction of 2,4,6-trimethoxy-vinylbenzene **1a** with hexamethylene tetraamine (HMTA) in TFA at 120 °C for 6 h resulted in the formation of the unexpected devinylated diformyl product **3a** and not the expected diformylation product **2a** as shown in Scheme 1. The formation of product **3a** occurred via tandem devinylation and diformylation reactions.

To optimize and explore the scope of this devinylation for a variety of substrates, first we sought to investigate reaction conditions for devinylation of **1a** by variation in standard Duff conditions. We conducted a series of controlled experiments as shown in Table 1. As depicted in Table 1, no thermal devinylation occurred in the presence of only acetonitrile solvent (entries 6 and 7). When the reaction was conducted using Duff reagent (HMTA/TFA) at room temperature, neither devinylation nor diformylation was observed (entry 2); however under reflux conditions, devinylated diformyl product **3a** was formed in excellent yield (entry 1). Further, in order to investigate the role of HMTA in devinylation, 2,4,6-trimethoxy-vinylbenzene **1a** was refluxed with TFA, which



Scheme 1. Devinylation of vinylbenzene **1a** under Duff reaction conditions.

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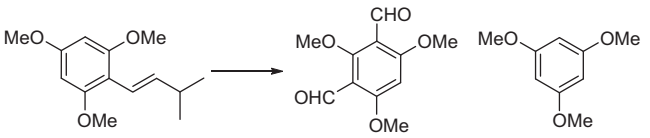
Table 1
Optimization of reaction conditions for devinylation[a]



Entry	Acid	Solvent	Reagent (if any)	Temp (°C)/time (h)	Product[b] (% yield)
1	TFA	TFA	HMTA	120/6	**3a** (84)
2	TFA	TFA	HMTA	25/6	**3a** (0)
3	TFA	TFA	None	120/6	**4a** (95)
4	TFA	TFA	None	25/6	**4a** (0)
5	None	ACN	None	25/6	**4a** (0)
6	None	ACN	None	90/6	**4a** (0)
7	None	ACN	None	120/6	**4a** (0)
8	$HClO_4$	$HClO_4$	None	120/6	**4a** (60)
9	pTSA[c]	ACN	None	90/6	**4a** (10)
10	pTSA[c]	ACN	None	120/6	**4a** (10)

[a] Reagents and conditions: **1a** (1 mmol), HMTA (4 mmol, wherever mentioned), acid and/or solvent (10 mL).
[b] Isolated yield.
[c] 50 mol % of pTSA.

led to the formation of devinylated product **4a** in 95% yield (entry 3). This result indicated that devinylation occurs in the presence of TFA under heating conditions and is independent of HMTA presence. Next we investigated whether devinylation occurs in the presence of acids other than TFA. The devinylated product **4a** was formed (60% yield) when **1a** was refluxed in the presence of perchloric acid (entry 8); however with pTSA, only >10% devinylated product was formed (entries 9 and 10).

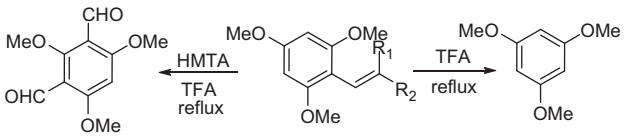
The scope of tandem devinylation–diformylation reaction[16] was then investigated for a variety of vinylbenzenes. Series of 2,4,6-trimethoxy-vinylbenzenes **1a**–**1j**[17,18] were prepared by Wittig reaction of 1-formyl-2,4,6-trimethoxy benzene with alkyl triphenyl phosphine salts. Under optimized Duff conditions, vinylbenzene **1a** produced 2,4-diformyl-1,3,5-trimethoxybenzene (**3a**) in 84% yield (Table 2, entry 1). Similarly various substituted short chain, long-chain, and branched dienyl 2,4,6-trimethoxy vinylbenzenes **1b**–**1j** participated well in this reaction producing exclusively 2,4-diformyl-1,3,5-trimethoxybenzene (**3a**) in 52–94% yield (entries 2–10). The synthesis of 2,4-diformyl 1,3,5-trimethoxy benzene (**3a**) was reported earlier from 1,3,5-trimethoxy benzene (**4a**) via double *ortho*-lithiation using *n*-BuLi–TMEDA complex.[19] As a control experiment for our study, we observed that **3a** can also be produced directly from **4a** using Duff reaction in 75% yield. Diformyl product **3a** finds utility for the preparation of novel macrocylic molecules such as tringlimines,[19] and a variety of polyformylated phloroglucinol class of natural products.[20]

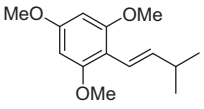
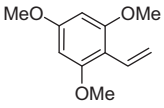
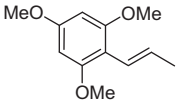
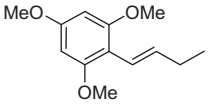
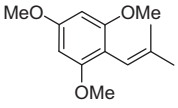
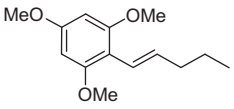
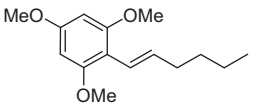
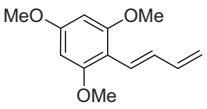
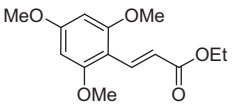
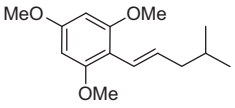
Similarly the scope of TFA mediated devinylation[21] of aromatic system was investigated for a variety of vinylbenzenes as depicted in Table 2. Like tandem devinylation–diformylation reaction, TFA-mediated devinylation product **4a** was formed in excellent yields from different vinylbenzenes.

To check whether this devinylation protocol works for aromatic systems other than 1,3,5-trimethoxybenzene, we conducted reaction of 3,4-dimethoxy styrene with TFA under optimized reaction conditions; however the desired devinylated product was not formed. Treatment of 3,4-dimethoxy styrene with Duff reagent was also not able to produce the expected devinylated product.

Next, we investigated the mechanism of devinylation of vinylbenzenes. For this reaction, we speculated two possible mechanisms, either free-radical or cationic mechanism. A free radical route should involve first the migration of vinylic double bond to form allyl group and then free-radical mediated allyl-elimination.

Table 2
Scope of the devinylation protocol for various vinylbenzenes[a,b]



Entry	Vinylbenzene	Product (% yield)[c] Duff condition[a]	Reflux in TFA[b]
1	 **1a**	**3a** (84)	**4a** (88)
2	 **1b**	**3a** (90)	**4a** (92)
3	 **1c**	**3a** (52)	**4a** (65)
4	 **1d**	**3a** (76)	**4a** (82)
5	 **1e**	**3a** (86)	**4a** (88)
6	 **1f**	**3a** (92)	**4a** (94)
7	 **1g**	**3a** (87)	**4a** (90)
8	 **1h**	**3a** (92)	**4a** (95)
9	 **1i**	**3a** (94)	**4a** (95)
10	 **1j**	**3a** (92)	**4a** (96)

[a] Reagents and conditions: **1** (1 mmol), HMTA (4 mmol) in TFA at 120 °C.
[b] Reagents and conditions: **1** (1 mmol) in TFA at 120 °C.
[c] Isolated yields.

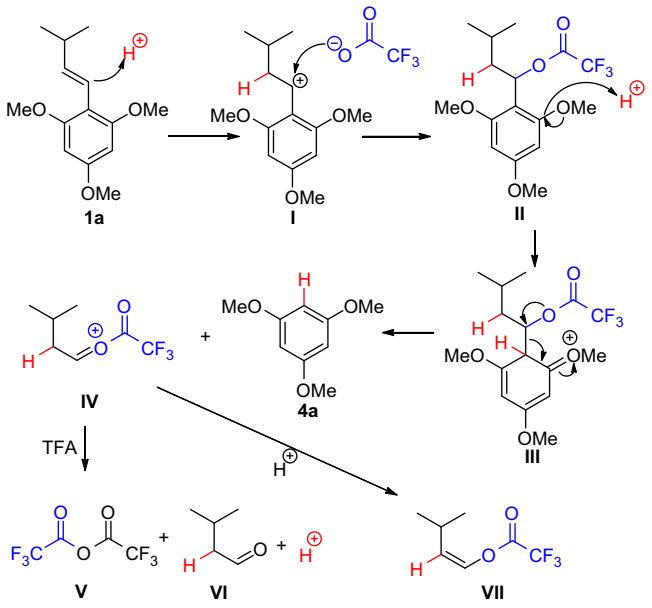


Figure 1. Plausible mechanism for TFA-catalyzed devinylation of vinylbenzenes.

Since we observed devinylation of vinylbenzene **1b** (where formation of allyl is not possible) under optimized reaction conditions (Table 2, entry 2), a mechanism involving the prior formation of allyl before elimination is not possible. Further, to confirm this, the reaction was performed in the presence of free-radical quencher TEMPO. Treatment of vinylbenzene **1a** with HMTA/TFA in the presence of TEMPO (10 mol %) produced desired diformyl product **3a**. Similarly, when vinylbenzene **1a** was treated with TFA in the presence of TEMPO (10 mol %) devinylated product **4a** was also produced in the desired yield. These results clearly indicate that devinylation process is independent of free-radical mechanism. Thus we propose that vinyl elimination must be proceeding via protonation of *ortho*-substituted OMe group. The plausible mechanism for TFA-catalyzed devinylation of vinylbenzenes involving the formation of protonated species **III**, which leads to elimination of vinyl functionality to produce **4a** is depicted in Figure 1. The depicted mechanism indicates the formation of volatile/base-sensitive side products **V**, **VI,** and **VII**, which explains why elevated temperatures drive this reaction.

In summary, we have reported a method for C-devinylation of aromatic systems for the first time. In addition, a facile and efficient protocol for tandem devinylation–diformylation of 2,4,6-trimethoxy-vinylbenzenes is also achieved. Devinylation protocol works well for a variety of vinyl substituents, however it is limited to only 1,3,5-trimethoxy benzene system. The developed protocol will be highly useful in the synthesis of the phloroglucinol class of complex natural products. With the discovery of facile C-devinylation method, vinyl functionality can be used as a protecting group in activated aromatic systems.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.064.

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16. Typical procedure for tandem devinylation–diformylation of 2,4,6-trimethoxy vinylbenzenes: To the solution of 2,4,6-trimethoxy vinylbenzene (**1a–1j**, 100 mg, 1 equiv) in TFA (2 ml) was added HMTA (4 equiv) and the resulting mixture was refluxed at 120 °C for 6–8 h. Completion of the reaction was monitored by TLC. Reaction mixture was cooled to room temperature and was neutralized with saturated $NaHCO_3$ solution and extracted with EtOAc (50 ml × 3). Combined organic layer was dried over anhydrous sodium sulfate and evaporated on vacuo rotavapor to get a crude product. The crude product was purified by silica gel (#100–200) column chromatography using 40% EtOAc:hexane as eluent to get **3a** in 85–96% yield. Product **3a** was characterized by comparison of melting point and NMR data with literature values. 2,4-Diformyl 1,3,5-trimethoxy benzene (**3a**): Light yellow solid; mp 70–72 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.33 (s, 2H), 6.28 (s, 1H), 4.13 (s, 6H), 3.95 (s, 3H); IR ($CHCl_3$): ν_{max} 3901, 3735, 3420, 2951, 2928, 2860, 1723, 1679, 1589, 1480, 1453, 1439, 1420, 1382, 1309, 1235, 1221, 1148, 1107, 1072, 1011 cm^{-1}; ESI–MS: *m/z* 225.07 $[M+H]^+$, 247.05 $[M+Na]^+$, 263 $[M+K]^+$; HRMS: *m/z* 225.0761 calcd for $C_{11}H_{12}O_5 + H^+$ (225.0757).
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21. General procedure for devinylation of 2,4,6-trimethoxy vinylbenzenes using TFA: The mixture of 2,4,6-trimethoxy-vinylbenzene (**1a–1j**, 100 mg) and TFA (10 ml) was refluxed at 120 °C for 6 h. After completion of the reaction, reaction mixture was cooled to room temperature, neutralized with saturated $NaHCO_3$ solution, and extracted with EtOAc (50 ml × 3). Combined organic layer was dried over anhydrous sodium sulfate and evaporated on vacuo rotavapor to get the crude product. Crude product was purified by silica gel (#100–200) column chromatography using 20% EtOAc: hexane as eluent to get **4a** in 82% yield. Product **4a** was characterized by comparison of TLC Rf value, melting point, and NMR data with commercially available sample (CAS # 621-23-8). 1,3,5-Trimethoxy benzene (**4a**): White crystalline solid; mp 52–54 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.08 (s, 3H), 3.76 (s, 9H); ESI-MS: *m/z* 169.01 $[M+H]^+$.