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Ortho-quinone methides: TFA-mediated generation in water and trapping with lactams and styrenes

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ABSTRACT

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Keywords: DFT TFA Vinylbenzenes Amidomethylation phenols in aqueous medium has been described. Developed protocol has a good substrate scope, involves mild reaction conditions and products are obtained in good yields. The quantum chemical calculations were performed in implicit solvent (water) conditions, which helped in tracing the reaction mechanism and getting insights on the possible reaction pathway, which involves the N-C bond formation and simultaneous hydrogen transfer to give final product. The applicability of this protocol for one-pot synthesis of flavans from phenols, formaldehyde and styrene has also been demonstrated.

A simple and efficient trifluroacetic acid mediated protocol for ortho-amidomethylation of

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Organic reaction in water has been an important area of interest in recent years to meet environmental considerations.¹ The use of water as a solvent contributes to environment friendly process.² For environmentally friendly processes, the "best solvent" is no solvent, but if required then water is recommended.³ In recent years, the major focus of process industries is to use water as a solvent rather than organic solvents.⁴ Mannich reaction is widely used for C-C bond formation and for the synthesis of enantiomerically enriched nitrogenous molecules including amino acids and amino alcohols.⁵ It is a classical method for the synthesis of β -amino ketones and aldehydes. Mannich reaction has been widely used in the synthesis of drugs and natural products containing nitrogen; due to which synthetic chemists are attracted towards this reaction.⁶ A lot of synthetic routes are reported for Mannich reaction including few reports on reaction in aqueous medium.⁷ Many reported reactions have been carried out in the presence of surfactant but normal phase separation is difficult due to the formation of emulsion because of surfactant.⁸ In continuation to our previous methodology on orthoamidoalkylation of phenols using Silica-HClO4 as a catalyst and acetonitrile as a reaction medium,⁹ we investigated this reaction using water as a reaction medium. Thus herein, we report an efficient, convenient and simple method for orthoamidomethylation of phenols using catalytic quantity of TFA in water as a reaction medium in place of Silica-HClO₄ (Figure 1). The use of N-vinyl lactam also produced the same orthoamidoalkylated product 1 via tandem devinylation followed by Mannich-type of condensation. Additionlly, herein we performed

quantum chemical calculations in implicit solvent (water) conditions in order to get insights on the possible reaction pathway.



Figure 1. TFA mediated *ortho*-amidomethylation of phenols in aqueous medium.

In order to establish a green protocol for ortho-amidomethylation of phenols, initially, a series of experiments were carried out using water as solvent with addition of various acids like formic acid, acetic acid and TFA (Table 1). In the presence of 10% formic acid in water under reflux condition, reaction proceeded, however there was only 60% conversion. Similarly, in case of acetic acid, reaction was incomplete. However, in the presence of

10% TFA in water, the reaction progress was better, producing 95% yield of the desired product. Further optimization of the TFA loading and reaction time indicated that 0.1% TFA in water for 0.5 h, was enough to get 95% yield of the product (entry 10 – optimized condition). The control reaction in water in the absence of acids does not proceed at all (entry 9). Next, we performed the reaction of phenol (**2a**) with formaldehyde and N-vinyl caprolactam using optimized reaction condition, which led to the formation of amido-alkylated product **1a** in 90% yield, through an initial N-devinylation.

Table 1. S	olvent a	nd cataly	st optimiz	ation	studies ^a
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	HCHO + HN	> —	- ()H	N
	2a 3 4a		~ 1a	\smile
Entry	Reaction medium	Temp. (°C) Time (h)	%Yield ^b
1.	10% AcOH in water	80	3	40
2.	10% HCOOH in water	80	4	60
3.	10% TFA in water	80	1	80
4.	10% TFA in water	25	4	0
5.	10% TFA in water	25	16	0
6.	1% TFA in water	80	2	80
7.	0.1% TFA in water	80	2	80
8.	0.1% TFA in water	80	1	78
9.	Water	80	24	0
10. ^c	0.1% TFA in water	80	0.5	95

^{*a*} Reagents and conditions: phenol **2a** (1.0 mmol), caprolactam **4a** (1.2 mmol), formaldehyde **3** (3.0 mmol); ^{*b*} isolated yield; ^{*c*} optimized reaction condition. All % values in reaction medium column are expressed as % v/v.

Next, we investigated the scope of this reaction for various substituted phenols and lactams. The substituted phenols as well as substituted phloroglucinols participated well in this reaction, producing corresponding Mannich products **1a-e** in excellent yields in a 30 min reaction time (Table 2).

Table 2. Scope of the reaction.





^a Reagents and conditions: phenol 2 (100 mg, 1.0 mmol), lactam
4 (1.2 mmol) or N-vinyl lactam 5 (1.5 mmol), formaldehyde 3 (3.0 mmol) in 0.1% TFA in water (10 mL); ^b isolated yield.

Next, the utility of this method for the synthesis of flavans was also investigated (Figure 2).¹⁰ Reaction worked very well with phenols as well as substituted phloroglucinols and styrenes producing corresponding flavans **6a-f** in 85 to 55% yields, respectively.



Figure 2. TFA catalyzed one-pot synthesis of flavans in aqueous medium. Reagents and conditions: (a) phenol 2 (100 mg, 1.0 mmol), styrene 7 (1.2 mmol), formaldehyde 3 (3.0 mmol) in 0.1% TFA in water (10 mL). Isolated yields are shown after compound codes.

To understand the mechanism of TFA-mediated orthoamidomethylation of phenols, quantum chemical studies on the reactants, intermediates, products and the important transition states of the reaction path have been carried out using B3LYP/6-311+G(d,p) method under implicit solvent (water) conditions. Figure 3 shows the reaction scheme along with the ΔG values and the activation barriers (E_a). Initially, the phenol **2b** after reacting with formaldehyde **3**, gives *O*-quinone methide **II**. Next, the coupling of intermediate **II** with lactam enol **4a1** proceeds via N-C bond formation and simultaneous hydrogen transfer (**II** + **4a**₁) to give the final product **1c** via **TS1**. The energy barrier for the proposed pathway is 11.1 kcal/mol. This step is exoergic by 24.0 kcal/mol and hence is quite readily favorable on kinetic as well as thermodynamic grounds.

In summary, we have developed an efficient, ecofriendly and catalyst-free TFA mediated protocol for ortho-amidomethylation of phenols. Flavans were also synthesized using this one-pot protocol. Quantum chemical calculations helped in tracing the reaction mechanism and provided further insights on possible reaction pathways.



Figure 3. Reaction mechanism for the TFA-mediated ortho-methylation. The Gibbs free energy values at each step were calculated using B3LYP/6-311+G(d,p) method under implicit solvent (water) conditions. All the energy values are given in kcal/mol.

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Supplementary material

Experimental details and spectral data scans. Supplementary data associated with this article can be found, in the online version at http://www.sciencedirect.com

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