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COMMUNICATION

Transition Metal-Free sp^3 C-H Functionalization of Arylacetic Acids for the Synthesis of 1,3,5-Triazines

Sachin D. Pardeshi,[a] Pratima A. Sathe,[a] Balu V. Pawar,[b] Kamlesh S. Vadagaonkar,[c]* and Atul C. Chaskar [a]*

Abstract: A one-pot simple, efficient and practically viable protocol for the synthesis of substituted 1,3,5-triazines has been reported from arylacetic acids and benzamidine hydrochloride. In addition, we demonstrated first transition metal free conversion of phenylacetic acid to benzaldehyde which on condensation with two moles of benzamidine hydrochloride offered 2,4,6-trisubstituted 1,3,5-triazines. This protocol is environmentally benign and economically viable which makes it feasible for gram scale synthesis.

Introduction

Heterocyclic compounds in general nitrogen heterocycles are incredibly diverse and received enormous attention over the past many decades owing to their promising potential applications. Indeed, among them 1,3,5-triazine moiety is widely explored as it is a part of many natural products and demonstrated broad spectrum of biological and medicinal activities *viz* antibacterial,[1] anti-inflammatory,[2] antimalarial,[3] antituberculosis,[4] antitumor agents[5] and inhibition of photosynthetic electron transport and binding.[6] Albeit, their unique properties made them useful as chelating ligands,[7] liquid crystals,[8] hydrogenation catalysis,[9] and Optical properties.[10]

These enormous significant applications have attracted the research community towards development of simple and economically viable methods for synthesis of 1,3,5-triazines. In last few years there are various methods have been developed by many researchers across the globe for the synthesis of 1,3,5-triazines. Many reports were found for the synthesis of 1,3,5-triazines which involve cyclotrimerization of nitriles.[11] In 1985, Saa et. al. used Fremy's salts with aromatic aldehydes for the synthesis of aryl-substituted s-triazines.[12] Xi and co-workers reported synthesis[13] and mechanistic studies[14] of triazines using 2,3-dialkyl-1,4-dilithio-1,3-dienes with nitriles in the presence of hexamethylphosphoramide (HMPA) while recently Majumdar et al. synthesized 1,3,5-triazines through copper-catalyzed cyclization of *N*-benzylbenzamidines in DMSO.[15] 2,4,6-Triphenyl-1,3,5-triazine have also been synthesized via oxidative cyclization of benzamidine hydrochloride with benzoyl isothiocyanate,[16] benzaldehyde,[17] benzyl alcohol,[18] toluene,[19] etc. (Figure 1). Jiang et al. used copper catalyst along with K_3PO_4 and O_2 as the oxidant through single-electron-transfer (SET) mechanism[20] whereas Bhanage et al. utilized PEG-600 in DMSO[21] and Cs_2CO_3 in TBHP[22] for the synthesis of 1,3,5-triazines from benzylamines and styrenes, respectively.

Nevertheless, these methods are associated with few shortcomings such as requirement of halogenated substrate, production of stoichiometric amount of undesirable waste, requirement of excess amines as co-catalyst, oxidation of aldehyde under normal environment and its decarboxylation at harsh reaction conditions. The C-H functionalization/activation received enormous attention in recent years due to their potential applications in synthesis of heterocyclic motiefs via selective construction of new C-C and C-heteroatom bonds. Indeed, its mechanistic understanding led to development of novel economically and environmentally benign synthetic protocols.

These matter of facts and our ongoing work[23] on the development of transition-metal free economically viable protocols for organic synthesis motivated us to use arylacetic acids as readily available stable starting material and potassium carbonate as inexpensive base which would lead to the development of scalable process for synthesis of aryl substituted 1,3,5-triazines

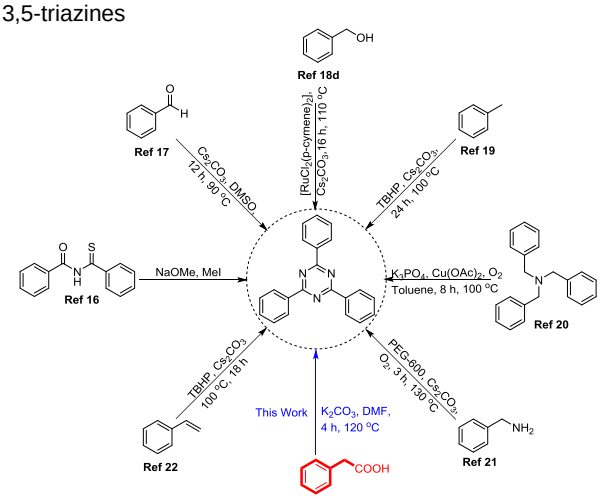

Figure 1. Methods for the synthesis of substituted triazines.

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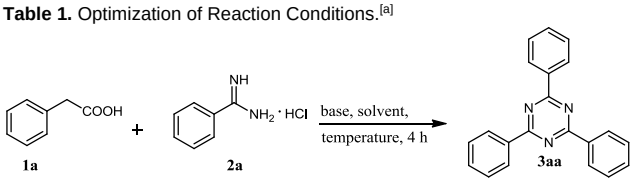
Results and Discussion

Table 1. Optimization of Reaction Conditions.[a]

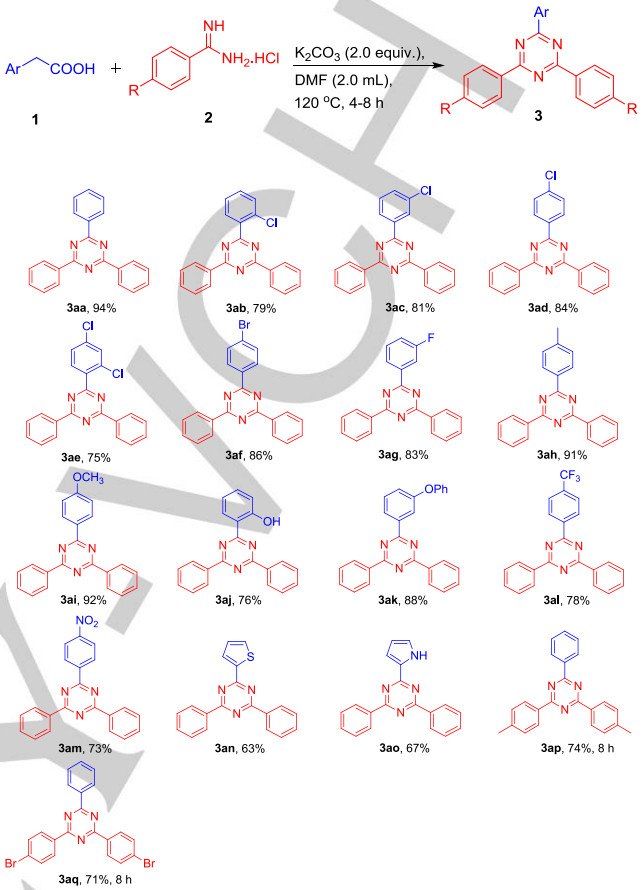


Entry	Base	Solvent[e]	Yield [%][b]
1	Cs_2CO_3	DMF	84
2	Na_2CO_3	DMF	82
3	CH_3COONa	DMF	85
4	**K_2CO_3**	**DMF**	**94**
5	K_2CO_3	DMSO	83
6	K_2CO_3	DPE	78
7	K_2CO_3	Xylene	n.d.
8	K_2CO_3	Toluene	n.d.
9	K_2CO_3	DMA	n.d.
10	K_2CO_3	TBHP	21
11	K_2CO_3	DMF	32[c] /61[d]

[a] Reaction conditions: phenylacetic acid **1a** (1.0 mmol), benzamidine hydrochloride **2a** (2.0 mmol), base (2.0 mmol), solvent (2.0 mL) were heated at 120 °C for 4 h. [b] Yield of isolated product after column chromatography. [c] Reaction performed at 90 °C. [d] Reaction performed at 100 °C. [e] Abbrevations: DPE = diphenyl ether, DMA = dimethylacetamide, TBHP = *tert*-butyl hydroperoxide

At the outset we began our investigation by exploring the model reaction of phenylacetic acid **1a** with benzamidine hydrochloride **2a** in basic medium. Substantially good yields of 1,3,5-triazine **3aa** was observed in the presence of base (2.0 equiv.) like Cs_2CO_3, Na_2CO_3 as well as NaOAc in *N*,*N*-dimethyl formamide (Table 1, entries 1-3). Notably, a highest yield of 94% was noticed in the presence of K_2CO_3 in DMF (Table 1, entry 4). Looking at the scope for improvement in the yield, screening of solvents was carried out. The reaction in DMSO and DPE offered 1,3,5-Triazine **3aa** in 83% and 78% yields, respectively (Table 1, entries 5 and 6). However, the reaction did not take place in the presence of xylene, toluene and *N*,*N*-dimethylacetamide (Table 1, entries 7-9) while, a very low yield of 21% was observed in TBHP (4.0 equiv.) (Table 1, entry 10). Next, we studied the effect of temperature on this reaction and found it detrimental as lower yields of product were obtained on decreasing the temperature (61% and 32% at 100 °C and 90 °C, respectively) (Table 1, entry 11).

Table 2. Scope of various arylacetic acids for the synthesis of 1,3,5-triazines.[a]



[a] Reaction conditions: arylacetic acid **1** (1.0 mmol), substituted benzamidine hydrochloride **2** (2.0 mmol), base (2.0 mmol), solvent (2.0 mL) were heated at 120 °C for 4-8 h.

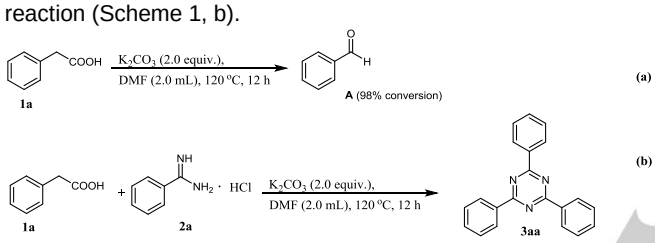
The scope and limitations of this method were explored by performing the reaction of various arylacetic acids **1** with benzamidine hydrochloride **2a** under the optimized reaction conditions (Table 2). Phenylacetic acid **1a** on reaction with benzamidine hydrochloride **2a** afforded 2,4,6-triphenyl-1,3,5-triazine **3aa** in 94% yield. Arylacetic acids bearing halogen substituents (2-Cl, 3-Cl, 4-Cl, 2,4-dichloro, 4-Br and 3-F) gave corresponding products **3ab-3ag** in good to excellent yields (75-83%). Similarly, arylacetic acids with electron-donating substituents (4-CH_3, 4-OMe, 2-OH and 3-OPh) produced respective 2,4,6-trisubstituted-1,3,5-triazines **3ah-3ak** in good yields (76-92%) while arylacetic acids bearing electron-withdrawing substituents such as 4-CF_3 and 4-NO_2 furnished the respective triazines **3al** and **3am** in 78% and 73% yields, respectively.

To extend the scope of the reaction, we next screened heteroarylacetic acids such as (2-(thiophen-2-yl)acetic acid and 2-(1*H*-pyrrol-2-yl)acetic acid and as expected these acids offered corresponding triazines **3an** and **3ao** in 63% and 67% yields, respectively under the optimized reaction conditions. We found that this method is robust and can tolerate various functional groups. This implies that the above mentioned protocol could be successfully applied for the large scale synthesis of various 1,3,5-triazines from diverse aryl/hetero acetic acids. In view of the broad

substrate scope, the present method was evaluated for the gram scale synthesis of 2,4,6-triphenyl-1,3,5-triazine. Gratifyingly, 1 g of phenylacetic acid produced 0.63 g of 2,4,6-triphenyl-1,3,5-triazine with a yield of 94% under the optimized reaction conditions. Thus, this protocol can be applied for the gram scale synthesis of 2,4,6-triphenyl-1,3,5-triazine.

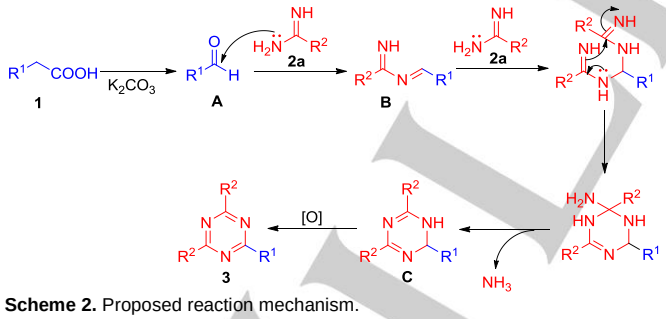
The scope of this reaction was extended by employing substituted benzamidine hydrochloride with phenylacetic acid. Phenylacetic acid **1a** on reaction with 4-methyl substituted benzamidine hydrochloride afforded corresponding product **3ap** in 74 % yield in 8 h.The reaction of phenylacetic acid **1a** with 4-bromobenzamidine hydrochloride occured smoothly to give corresponding product **3aq** in 71% yield in 8 h.

To gain more insight on the role of K_2CO_3 and endorse our hypothesis, a couple of control experiments were conducted (Scheme 1). Initially, when a mixture of phenylacetic acid (**1a**) and K_2CO_3 was heated in DMF at 120 °C for 12 h, 98 % conversion to benzaldehyde (**A**) was observed (Scheme 1, a). But, when the reaction of phenylacetic acid (**1a**) with benzamidine hydrochloride (**2a**) was performed in the presence of K_2CO_3, it went to completion in 4 h only, this implied that benzamidine hydrochloride (**2a**) playing a key role in accelerating the rate of reaction (Scheme 1, b).



Scheme 1. Control Experiments

On the basis of control experiments a plausible mechanism is depicted in Scheme 2. Initially, arylacetic acid (**1**) in the presence of K_2CO_3 undergoes oxidative decarboxylation to give aromatic aldehyde [**A**] which reacts with benzamidine hydrochloride (**2a**) and forms shiff base [**B**]. Intermediate [**B**] undergoes conjugate addition reaction with another molecule of benzamidine hydrochloride (**2a**) to give [**C**] which on oxidation offers desired product 1,3,5-triazine (**3**).



Scheme 2. Proposed reaction mechanism.

Conclusions

We have developed a one-pot, practical and environmentally benign synthesis of 1,3,5-triazines through sp^3 C-H functionalization of easily available arylacetic acids by using K_2CO_3 as a base. Use of inexpensive, transition metal-free reagent, broad substrate scope, good to excellent yields of products are notable features of this protocol. We strongly believe that this protocol will serve as an advancement to the existing method and will be widely used for the synthesis of biologically important 1,3,5-triazines.

Experimental Section

General Experimental Procedure for the Synthesis of 1,3,5-triazines

A round-bottom flask equipped with a magnetic stirring bar was charged with arylacetic acid (**1**) (1.0 mmol), K_2CO_3 (2.0 mmol) and DMF (2.0 mL) at room temperature. Substituted benzamidine hydrochloride (**2**) (2.0 mmol) was added to this mixture and the resulting mixture was heated at 120 °C for 4 to 8 h. The reaction progress was monitored by using TLC. After completion of the reaction, water was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (10 mLx3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by column chromatography on 60-120 mesh silica gel by using n-hexane:ethyl acetate (9:1) as the eluent to afford 2,4,6-trisubstituted-1,3,5-triazine (**3**).

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Keywords: Arylacetic acid • Benzamidine hydrochloride • K_2CO_3 • sp^3 C-H Functionalization • Transition metal-free

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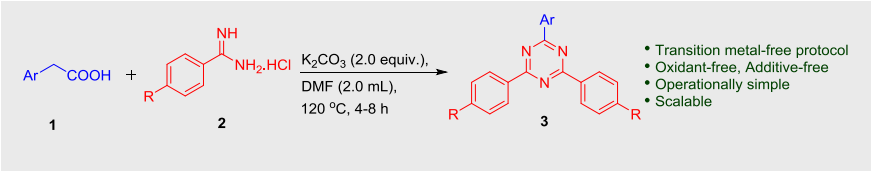

An efficient transition metal-free protocol for the synthesis of 1,3,5-trisubstituted triazines has been developed through C-H functionalization of arylacetic acids by using K_2CO_3 as a base, followed by condensation with substituted benzamidine hydrochloride.

*Transition metal-free, C-H Functionalization

Key Topic*

Sachin D. Pardeshi,[a] Pratima A. Sathe,[a] Balu V. Pawar,[b] Kamlesh S. Vadagaonkar,[c] and Atul C. Chaskar[a]**

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