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10.1002/ejoc.201800930

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Decarboxylative Arylation of α,β-Unsaturated Carboxylic Acids using Aryl Triazenes by Copper/Ionic Liquid Combination in PEG-400

Saurabh Kumar,^[a] Anand Kumar Pandey,^[a] Rahul Singh^[a] and Krishna Nand Singh^{[a],*}

Abstract: A practical method for the construction of stilbene derivatives has been developed *via* catalytic cross-coupling of cinnamic acids with aryl triazenes. The methodology offers high stereoselectivity, and is endowed with broad substrate scope, high yield, and significant functional group tolerance.

Introduction

Stilbenes are widely explored motifs present in natural products, pharmaceuticals and biological systems.^[1] They also serve as valuable synthetic intermediates for the preparation of many useful organic molecules owing to their propensity to participate in cycloaddition,^[2] cyclopropanation,^[3] and epoxidation reactions.^[4] Therefore, the synthesis and functionalization of stilbenes has perpetually attracted a great deal of interest of organic chemists.

The Wittig reaction, Julia olefination and Peterson reaction employing phosphonium salts or organometallic starting materials are amongst the most prominent and extensively used synthetic approaches to achieve diverse alkene derivatives. Alternatively, the semihydrogenation of alkynes may also be utilized to accomplish stilbene derivatives.^[5] The transitionmetal-catalyzed Heck-type reaction is another powerful way for preparing stilbene derivatives using alkenes,^[6] nitroalkenes,^[7] vinyl halides,^[8] vinylic ethers,^[9] boronic acids,^[10] and cinnamic acids.[11] Some notable recent advances for their synthesis are outlined in Scheme 1. Despite considerable progress over the years, the existing methods still suffer from certain drawbacks, such as use of expensive materials, harsh conditions, and requirement for an inert conditions. Thus from the above perspective, there stands enough scope for further exploration and necessity to develop new and useful protocols to simplify the synthesis of stilbene motifs.

Decarboxylative cross-coupling reactions have attained the repute of a proficient strategy for the creation of a variety of C–C and C–heteroatom bonds, owing to their prospective use in stepeconomic, environmentally benign, and regio- and stereo-selective synthesis.^[12] Also the ready commercial availability, ample structural diversity apart from easy preparation *via* a range of well established protocols, and ease to store and

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handle, render the carboxylic acids a valuable starting material in organic transformations.^[13]

Aryl triazenes have been recently employed for certain cross coupling reactions owing to their identical acceptability to the corresponding arenediazonium salts, and are known to have rather better stability under ambient conditions lending them an edge over the later.^[14]

Previous Reports

Ar¹

(i) Goossen et. al, J. Am. Chem. Soc., 2007, 129, 4824

COOH + Ar²-X
$$\xrightarrow{\text{N-ligand}}_{\text{K}_2\text{CO}_3}$$
 Ar¹ Ar²

(ii) Schroll et. al, ChemistryOpen, 2012, 1, 130

Ar¹
$$Z$$
 + Ar²-N₂BF₄ $Ru(bpy)_3^{2+}$ Ar¹ Ar²
Z= H, COOH, NO₂ DMSO blue light

(iii) Zhang et. al, Chem. Commun., 2016, 52, 14234

$$r^{1}$$
 NO₂ + Ar²-N₂BF₄
DMF
green LEDs Ar¹ Ar²

Our Approach

А

$$Ar^{1}$$
 COOH + $N_{N^{2}}N_{Ar^{2}}$ $\frac{Cu(OAc)_{2}H_{2}O}{IL1, PEG-400}$ Ar^{1} Ar^{2}



lonic liquids have been identified as potential alternative reaction medium, and are endowed with green features like non-volatility, non-flammability, thermal stability and recyclability.¹⁵ Brønsted acidic ionic liquid (BAIL)-promoted synthetic protocols have drawn major industrial and academic interest with adjustable acidity, easy recyclability and their dual role as catalyst as well as reaction medium.¹⁶ Accordingly some acidic ILs (Figure 1) have been prepared and subjected to the studies undertaken.

In order to avoid the hazards associated with the commonly used organic solvents, organic chemists have always been tempted to accomplish the synthesis in environmentally benign solvents with lower volatility and less toxicity. Polyethylene glycol (PEG) is one of the most desirable reaction media to overcome the concerns of organic solvents, as it is thermally stable, easily recoverable and nontoxic, thereby reassuring the synthetic protocols.^[17]

Our group has recently explored the scope of decarboxylative strategy for the synthesis of vinyl sulfones, *N*-acylated indoles, 2-substituted benzothiazoles, thioamides and α,β -epoxy ketones, using easily accessible α,β -unsaturated carboxylic acids as functional surrogate to the corresponding alkenes as well as alkynes.^[18]

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Figure 1. Acidic ionic liquids (AILs) examined.

In order to further explore the scope of decarboxylative strategy, we envisaged and realized a stereoselective synthesis of stilbenes through decarboxylative aryation using cinnamic acids and aryl triazene as vinyl and aryl surrogates respectively in an environmentally benign medium (Scheme 1).

Results and Discussion

To begin with, a model reaction employing cinnamic acid (1a) and 1-(p-tolyldiazenyl)pyrrolidine (2a) was screened thoroughly by varying different parameters such as catalyst, acidic ionic liquid, solvent, temperature, and time (Table 1). The initial reaction conditions using equimolar quantities of both the reactants and 1-methylimidazolium hydrogen sulfate (IL1) without a catalyst in acetonitrile at 70 °C for 24 h failed to yield the desired product. After that, different transition metal catalysts (20 mol%) viz., NiCl₂.6H₂O, FeCl₃, CoCl₂.6H₂O and Cul were added to screen their catalytic efficacy (entries 2-5), which revealed Cul as the only hit to afford 28 % product yield. Then were used some other copper salts such as CuCl, CuBr, CuBr₂ Cu₂O and CuCl₂.2H₂O (entries 6–10), but yet no significant observation was made. However to our utmost delight, the use of Cu(OAc)₂ and Cu(OAc)₂.H₂O enhanced the yield considerably to 63 % and 68 % respectively (entries 11 & 12). Maintaining other parameters of the entry 12 intact, the effect of different solvents was afterward examined (entries 13-20). Markedly high product vields were observed with MeOH. EtOH. PEG-400 and PEG-600, with PEG-400 as the top one (entry 19). Notably, the reaction could not succeed in the absence of the acidic ionic liquid (entry 21) demonstrating the inevitability of the acidic ionic liauid.

Other acidic ionic liquids IL2, IL3, IL4, IL5, IL6 and IL7, when tried, could not provide the product in appreciable yields (entries 22-27). The catalyst loading required was also studied, which disclosed that an increase in the concentration upto 40 mol% could not bring about any sizable lead, while lowering the concentration to 10% lowered the product yield considerably.

Thus the best set of reaction conditions (entry 19) comprised of 20 mol% of $Cu(OAc)_2$. H_2O assisted by **IL1** in PEG 400 at 70 °C under open atmosphere.

able 1. Optimization of reaction conditions. ^[a]							
En	try	Catalyst (20 mol %)	Promoter	Solvent	Yield(%) ^[b]		
1			1	CH-CN	0		
2	,	NiCla 6HaO	II 1		0		
		FeClo	1	CH ₂ CN	ů 0		
4	L		.∟. II 1	CH ₂ CN	0		
-		Cul	.⊑.ı II 1	CH ₂ CN	28		
6	,. ,	CuBr	1	CH ₂ CN	20		
7	,	CuCl	1		25		
۶		CuBro	.∟.		39		
ç)		 II 1	CH ₂ CN	27		
1	0.	CuCl ₂ ,2H ₂ O	IL1	CH ₂ CN	58		
1	1.	Cu(OAc) ₂	IL1	CH₃CN	63		
1	2.	Cu(OAc) ₂ .H ₂ O	IL1	CH ₃ CN	68		
1	3.	Cu(OAc) ₂ .H ₂ O	IL1	Toluene	15		
1-	4.	Cu(OAc) ₂ .H ₂ O	IL1	DCE	35		
1	5.	Cu(OAc) ₂ .H ₂ O	IL1	DMSO	40		
1	6.	Cu(OAc) ₂ .H ₂ O	IL1	DMF	12		
1	7.	Cu(OAc) ₂ .H ₂ O	IL1	MeOH	76		
1	8.	Cu(OAc) ₂ .H ₂ O	IL1	EtOH	82		
1	9.	Cu(OAc) ₂ .H ₂ O	IL1	PEG-400	86		
2	0.	Cu(OAc) ₂ .H ₂ O	IL1	PEG-600	76		
2	1.	Cu(OAc) ₂ .H ₂ O		PEG-400	0		
2	2.	Cu(OAc) ₂ .H ₂ O	IL2	PEG-400	42		
2	3.	Cu(OAc) ₂ .H ₂ O	IL3	PEG-400	66		
2	4.	Cu(OAc) ₂ .H ₂ O	IL4	PEG-400	15		
2	5.	Cu(OAc) ₂ .H ₂ O	IL5	PEG-400	60		
2	6.	Cu(OAc) ₂ .H ₂ O	IL6	PEG-400	40		
2	7.	Cu(OAc) ₂ .H ₂ O	IL7	PEG-400	trace		

^[a]Using **1** (1.0 mmol), **2** (1.0 mmol), catalyst (20 mol%), ionic liquid (1 equiv.), solvent (1 mL) in open vessel at 70 °C for 24 h.

^[b]Isolated yield after flash column chromatography.

Pyrrolidine was also replaced by different secondary amines *viz.* piperidine, morpholine and diethyl amine, and the resulting triazenes were subsequently allowed to undergo the reaction with cinnamic acid. However, pyrrolidine remained to be the best choice to afford the maximum yield of the product (Scheme 2).



Scheme 2. Reaction of different triazene derivatives with cinnamic acids.

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With the established conditions in hand, the versatility of the reaction was examined using a variety of cinnamic acids and aryl triazenes with different substitution patterns. The outcome is given in Table 2. Both the reacting partners containing different electron-withdrawing as well as electron-donating substituent participated nicely in the reaction and offered the desired products 3a-3x in reasonably good to high yields. Aryl triazenes containing electron rich substituent in particular provided higher yields. A number of substituent viz., CH₃, CI, F, OMe, NO₂, CF₃, CN, and COOMe were well tolerated during the course of reaction. o-Chlorocinnamic acid afforded somewhat low product yield (3d, 71%) perhaps due to steric reason. The reaction was also extended to a heteroaromatic (E)-3-(thiophen-2-yl)acrylic acid to afford the products 3k and 3l. 1-(Naphthalen-1yldiazenyl)pyrrolidine also underwent the reaction smoothly to give the product 3s in fairly high yield.

Table 2. Scope and versatility of the reaction.





^[a]Using **1** (1.0 mmol), **2** (1.0 mmol), Cu(OAc)₂·H₂O (20 mol%), **IL1** (1 equiv.), PEG-400 (1mL) in open vessel at 70 °C for 24 h. ^[b]Isolated yield after flash column chromatography.

To get an insight into the reaction mechanism, a number of control experiments were carried out (Scheme 3). The model reaction between **1a** and **2a** under the standard conditions remained almost unaffected in the presence of radical scavengers like TEMPO and BHT, thereby excluding the possibility of a radical pathway. The reaction of a representative diazonium salt namely *p*-methoxybenzenediazonium tetrafluoroborate (**4a**) instead of aryl triazene, with **1a**, also gave rise to the corresponding product (**3r**, 79%), suggesting an

intermediacy of the arenediazonium cation during the course of reaction.



Based on the existing literature,^[19–22] control experiments and isolation of products, a plausible mechanism is outlined in Figure 2. The reaction is assumed to proceed *via* a copper carboxylate intermediate I, which undergoes decarboxylation to provide the organo-copper intermediate II. Ionic liquid (IL1)assisted generation of the arenediazonium cation (4) from aryl triazene (2) finally couples with the intermediate II to give the intermediate III and sets the stage for the reductive elimination, which regenerates the catalytic copper acetate by aerial oxidation of Cu(I) species to Cu(II) along with the final product 3.



Figure 2. Plausible reaction mechanism.

Conclusions

In conclusion, a practical approach involving decarboxylative arylation of cinnamic acids using aryl triazenes has been developed to accomplish the synthesis of synthetically and biologically important stilbenes by copper/lonic Liquid combination in PEG-400. The method is versatile and offers high yield, broad substrate scope and good functional group tolerance.

Experimental Section

A mixture of cinnamic acid (1, 1.0 mmol), aryl triazene (2, 1.0 mmol), $Cu(OAc)_2$.H₂O (20 mol%), **IL1** (1.0 equiv.) and PEG-400, placed in a 10– mL borosilicate vial, was stirred under open atmosphere at 70° C for 24 h. After completion of the reaction (monitored through TLC), the mixture was worked–up using water–ethyl acetate. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude product was finally purified by Flash chromatography using n–hexane and ethyl acetate as eluent.

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We are thankful to the CSIR, New Delhi (Project No. 02(0258)/16/EMR-II) for financial assistance, and for SRF to SK.

Conflict of interest

The authors declare no conflict of interest.

Keywords: Decarboxylative coupling • Stilbenes • Aryl triazenes • Copper catalysis • Ionic Liquid

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Decarboxylative Arylation of α , β -Unsaturated Carboxylic Acids using Aryl Triazenes by Copper/Ionic Liquid Combination in PEG-400

Decarboxylative Arylation: A practical approach involving decarboxylative arylation of cinnamic acids using aryl triazenes has been developed to accomplish the synthesis of stilbenes. The method employs easily accessible starting materials, and is endowed with broad substrate scope and functional group tolerance.

Yield upto 86% 24 examples

Cu(OAc)

Ionic Liquid PEG-400 70 °C, 24 h