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Synthesis of Substituted Nitroolefins: A Copper Catalyzed Nitrodecarboxylation of Unsaturated Carboxylic Acids[†]

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A novel, mild and a convenient method for the nitrodecarboxylation of substituted cinnamic acid derivatives to their nitroolefins is achieved using catalytic amount of CuCl (10 mol%) and tert-butyl nitrite (2 equiv) as a nitrating 10 agent in the presence of air. This reaction provides a useful method for the synthesis of β , β -disubstituted nitroolefin derivatives, which are generally difficult to access from other conventional methods. Additionally, this reaction is selective as E-isomer of acid derivatives furnish the corresponding E-15 nitroolefins. One more salient feature of the method is, unlike other methods, no metal nitrates or HNO₃ are employed for the transformation.

In recent times, decarboxylative coupling reactions have emerged as a powerful tool for C-C¹ bond and C-hetero² bond forming 20 reactions. By adopting the decarboxylative coupling strategy, a variety of aromatic acids and acrylic acids were coupled with aromatic halides^{3a} or triflates,^{3b} hydrocarbons,^{3c} alcohols,^{3d} ethers^{3d} etc.¹ to obtain a variety of compounds including olefin derivatives. Nitroolefins represent a unique class of nitro ²⁵ compounds, which have multifaceted utility in organic synthesis.⁴ Besides their applications in pharmaceuticals,⁵ they serve as important precursors in organic synthesis.⁴ β -monosubstituted nitroolefins and β , β -disubstituted nitroolefins also serve as vital precursors for catalytic asymmetric conjugate addition⁶ and ³⁰ asymmetric hydrogenation⁷ to furnish optically active, synthetically valuable products.8 Henry reaction of condensing aldehydes with nitroalkanes is one of the general methods to access conjugated nitroolefins.9 Nitration of alkenes is another useful method for synthesizing nitroolefins.¹⁰ Although 35 decarboxylative nitration is known in literature, it was achieved using harsh reaction conditions such as high temperature,^{11a} or highly acidic reaction conditions (HNO3),116-d or using stoichiometric amounts of metal nitrates.^{11e-i} Due to these reasons, these strategies have restricted the scope of reactions

- 40 and lack of compatibility with oxidizable and/or acid sensitive functional groups. To overcome these limitations, mild and convenient methods to access nitroolefins are well sought. As cinnamic acid and its derivatives are easily available or synthesized the nitrodecarboxylation of cinnamic acid and its
- 45 derivatives serve as a convenient and attractive procedure for the synthesis of corresponding nitroolefins. Although, nitroolefins are synthesized from their corresponding olefins, the isolation of such olefins is a cumbersome task, due to their volatile nature,

which is a one of the major limitations associated with these 50 methods. The decarboxylation of cinnamic acid is generally

Table 1. Screening studies

Ph Ph 1	соон	+ TBN	Catalyst Oxidant Solvent, Ter	──► np Ph´	Ph NO ₂ 2a
entry	TBN	catalyst	oxidant	solvent	yield ^a
	(equiv)	(10 mol%)		(°C)	(%)
1	1.5	CuCl	O ₂	CH ₃ CN (rt)	34
2	1.5	CuCl	O ₂	CH₃CN (60)	66
3	1.5	CuCl	O ₂	CH ₃ CN (80)	77
4	1.5	CuCl	O ₂	CH ₃ CN (80)	83
5	2.0	CuCl	air	CH₃CN (80)	96
6	2.0	CuCl	air	CH ₃ CN (80)	82 ^b
7	2.0	none	air	CH ₃ CN (80)	44
8	2.0	Cul	air	CH ₃ CN (80)	90
9	2.0	$CuCl_2 \cdot 2H_2O$	air	CH ₃ CN (80)	83
10	2.0	Cu(ClO ₄)·6H ₂ O	air	CH ₃ CN (80)	86
11	2.0	Cu(OTf) ₂	air	CH ₃ CN (80)	77
12	2.0	CuCl	air	DCE (80)	50
13	2.0	CuCl	air	THF (80)	72
14	2.0	CuCl	air	Toluene (80)	70
15	2.0	CuCl	air	DMF (80)	trace
16	2.0	CuCl	air	H ₂ O (80)	nd

^a Isolated yields. ^b 5 mol % of CuCl.

performed using copper salt of cinnamic acid followed by quenching with suitable radical partner.3c,3d tert-Butyl nitrite (TBN) is a mild, and commercially available nitrating reagent which is easy to handle, and is known to generate nitro radical in 60 the presence of air^{12a,12b,} or oxygen.^{12c,12d} In this context, we envisioned a reaction of α , β -unsaturated acid with Cu salt and TBN in the presence of air to obtain the corresponding nitro compound. In this direction, and in continuation of our studies on the utility of copper catalysts for C-N bond forming reaction,¹³ 65 herein we present a novel, mild method to synthesize a variety of β -monosubstituted and β , β -disubstituted nitrolefins by employing catalytic amount of CuCl with TBN in the presence of air.¹⁴

 β,β -Disubstituted nitrolefins are synthetically valuable precursors, which cannot be easily synthesized by conventional 70 Henry reaction.^{9,7a,7c} Due to this consideration, the preliminary

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investigations were undertaken by reacting 3,3-diphenylacrylic acid (1a) with Cu catalysts using TBN as a nitrating agent in the presence of air or oxygen (Table 1). As revealed by these studies, the combination of catalytic amount of CuCl with TBN, in the presence of air use good abaies to offset this transformation

- ⁵ presence of air was good choice to affect this transformation (entries 1-5, Table 1). The optimal reaction conditions for this transformation was achieved by performing the reaction of **1a** with TBN (2 equiv) and CuCl (10 mol%), in CH₃CN at 80 °C (entry 6, Table 1). Lowering the catalyst (CuCl) loading to 5 mol
- ¹⁰ % resulted in decreasing the yield of the product (entry 7). Interestingly, the reaction also proceeded in the absence of copper catalyst to furnish the product **2a** in low yield (44%, entry 8). Further, it was also found that other copper catalysts such as CuI, CuCl₂ \cdot 2H₂O, Cu(ClO)₄ \cdot 6H₂O, Cu(OTf)₂ were useful for this
- ¹⁵ transformation, as these reactions resulted in the formation of **2a** in good yields (77-90%, entries 9-12). The solvent screening studies indicated that the solvents such as THF, toluene and dichloromethane were useful but resulted in formation of product in low yields (entries 13-15) while the reaction did not proceed in ²⁰ DMF or water (entries 16-17).

Table 2 Nitrodecarboxylation of β -alkyl cinnamic acids to β -alkyl nitroolefins



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The scope of the copper catalyzed nitrodecarboxylation was further examined with β , β -disubstituted acrylic acid derivatives Table 2). (*E*)-3-Phenylbut-2-enoic acid on treatment with 2 equiv of TBN in the presence of 10 mol% CuCl in CH₃CN underwent a ³⁰ smooth transformation to (*E*)-(1-nitroprop-1-en-2-yl)benzene (**2b**) in 71% isolated yield. (*E*)-1-methyl-4-(1-nitroprop-1-en-2yl)benzene furnished the corresponding nitroolefin **2c** in 74%. While, (*E*)-3-(4-methoxyphenyl)but-2-enoic acid and (*E*)-3-(4-

- bromophenyl)but-2-enoic acid under the similar reaction ³⁵ conditions resulted in the formation **2d** and **2e** in moderate yields (52%). β -Alkyl substituted naphthalene derivative such as (*E*)-3-(naphthalen-2-yl)but-2-enoic acid underwent the nitrodecarboxylation reaction to form the corresponding nitro derivative **2f** in 70%. The heterocyclic α , β -unsaturated acid such
- ⁴⁰ as (*E*)-3-(thiophen-2-yl)but-2-enoic acid was successfully transformed in to its nitroolefin **2g** in moderate yield (52 %). The reaction of (*E*)-3-(pyridin-2-yl)but-3-enoic acid with TBN and CuCl was interesting, as the reaction produced the mixture of 2-(3- nitroprop-1-en-2-yl)pyridine (**2ha**) and (*E*)-2-(1-nitroprop-1-45 en-2-yl)pyridine (**2hb**) in 80% yield with **2ha** in major amount

(60:40 ratio of **2ha** and **2hb**). The formation of 2-(3-nitroprop-1en-2-yl)pyridine (**2ha**) as a major product can be explained on the basis of isomerization of **2hb** to **2ha**, which can be view Article online the coordination of copper metal to the adjacent methyl group to form 5 membered complex. Additionally, the nitrodecarboxylation reaction is selective as *E*-isomer of acids resulted in the formation of the corresponding *E*-nitroolefins.

Table 3 Nitrodecarboxylation of α , β -unsaturated acid to nitroolefins



^a Reaction conditions: acid (0.50 mmol), TBN (1.0 mmol), CuCl (0.05 mmol), air, CH₃CN (2 ml). ^b Isolated yield. ^c used 4 equiv of TBN

The scope of this reaction was further expanded by investigating the reaction of a variety of cinnamic acid 60 derivatives and results are compiled in Table 3. As can be seen in Table 3, a variety of substituted cinnamic acid derivatives such as (E)-3-(4-methoxyphenyl)acrylic acid, and (E)-cinnamic acid reacted well with TBN in the presence of CuCl to furnish corresponding nitro derivatives 3a and 3b in excellent yields 65 (92% and 82% respectively). (E)-3-(p-tolyl)acrylic acid under the similar reaction conditions afforded **3c** in moderate yield (52%). Similarly, (E)-3-(naphthalen-1-yl)acrylic acid reacted well to furnish the product 3d in 91% yield, whereas (E)-3-(3,4dimethoxyphenyl)acrylic acid (E)-3-(4and 70 (benzyloxy)phenyl)acrylic acid furnished 3e and 3f in 69% and 60% respectively. As can be seen, the reaction of (E)-3-(3phenoxyphenyl)acrylic acid needed excess of TBN (4 equiv) to furnish (E)-1-(2-nitrovinyl)-3-phenoxybenzene **3g** in 84%. Whereas the reaction of (E)-3-(4-(trifluoromethyl)phenyl)acrylic 75 acid, and (E)-3-(4-cyanophenyl)acrylic acid with excess of TBN (4 equiv) did not affect the yields of the products (E)-1-(2nitrovinyl)-4-(trifluoromethyl)benzene (3h, 46%) and (E)-4-(2-

^aReaction conditions: acid (0.50 mmol), TBN (1.0 mmol), CuCl (0.05 25 mmol), air, CH₃CN (2 ml). ^bIsolated yield.

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nitrovinyl)benzonitrile (**3i**, 36%). Further, (*E*)-3-(2bromophenyl)acrylic acid, (*E*)-3-(2-fluorophenyl)acrylic acid, and (*E*)-3-(4-chlorophenyl)acrylic acid under the optimized conditions furnished the corresponding nitroolefins **3j**, **3k** and **3l** s in moderate to good yields (45%, 68%, and 50% respectively, Table 3). It worth noting that acid sensitive substrates such as

- furan and thiophene derivatives sustained very well under the reaction conditions. As can be seen, the reaction was facile with heterocyclic α , β -unsaturated acids, (*E*)- 3-(Thiophen-2-¹⁰ yl)acrylic acid to furnish corresponding nitro derivative, (*E*)-2-(2-
- nitrovinyl)thiophene (**3m**, 72% yield), whereas the similar reaction with (E)-2-(2-nitrovinyl)thiophene (**3m**, 72% yield), whereas the similar reaction with (E)-3-(furan-2-yl)acrylic acid resulted in the formation of (E)-2-(2-nitrovinyl)furan (**3n**) in 41%. These nitration reaction catalysed by CuCl appears to be versatile as
- is indole acrylic acid such as (E)-3-(1-benzoyl-1H-indol-2yl)acrylic acid under the optimal reaction conditions furnished the corresponding nitroolefin **30** in good yield (75%). As the reaction was proceeding readily with cinnamic acid, we thought it would be interesting to subject dienoic acid for the nitrodecarboxylation
- ²⁰ reaction. Hence, the reaction of (2*E*,4*E*)-5-phenylpenta-2,4dienoic acid under optimal conditions resulted in the formation of corresponding nitroolefin, ((1*E*,3*E*)-4-nitrobuta-1,3-dien-1yl)benzene **3p** in 34%. Our attempts to convert (*E*)-4-(2carboxyvinyl)benzoic acid, 2-cyclohexylideneacetic acid, 4-²⁵ methoxybenzoic acid to their corresponding nitroolefins did not meet with success and the starting materials were recovered unchanged. The inertness of these acids for nitrodecarboxylation can be attributed to the inability of carboxylic acid salts of aromatic and aliphatic acids to undergo decarboxylation under the ³⁰ present reaction conditions.



Scheme 1 Control experiments

To follow the reaction pathway, few control experiments were ³⁵ performed (Scheme 1). The reaction of 3,3-diphenylacrylic acid (1a) with CuCl (10 mol %), and TBN (2 equiv) in CH₃CN was performed under the optimal conditions in the presence of radical inhibitors such as TEMPO (2,2,6,6-tetramethylpiperidin-1yl)oxyl) and BHT (butylated hydroxytoluene). As can be seen, ⁴⁰ the reaction in the presence of TEMPO has drastically reduced the yield of **2a**, whereas the similar reaction in the presence of BHT did not proceed. These observations indicate that the reaction may be proceeding through a radical intermediate. Based on this information, and literature precedence,^{3d} a tentative ⁴⁵ mechanism is proposed (Scheme 2). α , β -Unsaturated acid reacts with CuX to form the corresponding Cu (II) salt, which further

reacts with nitro radical, (which is generated by the reaction of TBN in the presence of air) to form radical I. Further I

undergoes decarboxylation to form the corresponding nitroolefin.



Scheme 2. Tentative Mechanism

Conclusions

In conclusion, we report a novel, mild and a convenient method for the nitrodecarboxylation of substituted cinnamic acid ⁵⁵ derivatives to their correponding nitroolefins catalyzed by CuCl in the presence of air. This nitrodecarboxylation reaction uses TBN as a nitrating source. Besides these advantages, the reaction provides a useful method for the synthesis of β , β -disubstituted nitroolefin derivatives, which are generally difficult to access ⁶⁰ from other conventional methods. Additionally, this reaction is selective as *E*-isomer of acid derivatives resulted in the formation of the corresponding *E*-nitroolefins. Apart from these advantages, metal nitrates or HNO₃ are not employed for the transformation. One more salient feature of this reaction is that the acid sensitive

65 functionalities or compounds such as nitrile functionality and thiophene and furan derivatives are well tolerated under the reaction conditions.

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Notes and references

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