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COMMUNICATION

Silver catalyzed decarboxylative acylation of pyridine-*N*-oxides using α-oxocarboxylic acids

Rajendran Suresh,[a,b] Rajendran Senthil Kumaran,[b] Vajiram Senthilkumar[b] and Shanmugam Muthusubramanian,*[a]

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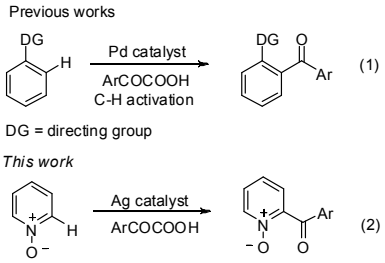
Abstract: Silver catalyzed acylation of pyridine-*N*-oxides by α-oxocarboxylic acid is demonstrated. This decarboxylative acylation using a metal catalyst takes place at 50 °C *via* a radical process.

Transition metal catalyzed decarboxylative coupling has developed as a powerful strategy for establishing various carbon-carbon and carbon-heteroatom bond formations over the past few years.[1] Numerous efforts have been devoted in this area which led to the development of efficient synthesis of valuable derivatives.[2] Relatively unexplored decarboxylative coupling of α-oxocarboxylic acid has started receiving considerable attention.[3,4] Decarboxylation of this acid generates an acyl surrogate which can be linked to a coupling partner by a metal catalyst. Unsymmetrical heteroaryl aryl ketone is an important structural unit found in biologically active and medicinally relevant compounds.[5] This skeleton, which is hard to acquire in a single step by other means, can be rapidly accessed. Goossen initiated such a study by coupling the α-oxocarboxylic acid with aryl bromide using Cu/Pd bimetallic catalyst system.[3a] Recently, Pd(II)-catalyzed decarboxylative acylation of potassium aryltrifluoroborate at ambient temperature has been reported.[3b] Following the early reports, various decarboxylative coupling of α-oxocarboxylic acid were surfaced in the literature and they were all mainly based on C-H activation method due to its high atom and step economy.[6] Ge demonstrated the palladium catalyzed decarboxylative *ortho*-acylation of acetanilide with α-oxocarboxylic acid at room temperature.[4a] Subsequently, acylation of 2-phenylpyridine was reported using the same strategy.[4b] Meanwhile, Zhang used 2-phenoxypyridine for the decarboxylative acylation and disclosed that pyridine can be removed easily after acylation to obtain 2-hydroxyaryl ketone.[4c] Decarboxylative acylation of cyclic enamide[4d] was also attempted at room temperature, which was proved to be effective on phenylacetamide as well.[4e] Recently, Tan and Kim independently described the decarboxylative ortho-acylation on O-methyl aldoxime and ketoxime respectively.[4f,g] Despite the fact that both

Figure 1 Decarboxylative acylation



substrates underwent smooth acylation, the acylation of *O*-methyl aldoxime was found to take place at a milder condition. Very recently, azoxybenzene was successfully used for this investigation by Wang.[4h] Interestingly, Pd-catalyzed chemoselective *ortho*-acylation of benzoic acid was achieved by the decarboxylative coupling of α-oxocarboxylic acid, wherein the former acid group acted as a directing group and also remained intact at the end of the reaction.[4i] Though the acylation of arenes with the assistance of directing group have been disclosed (Figure 1; equation 1), acylation of pyridine *N*-oxide has been not addressed so far in the literature (Figure 1; equation 2).

Pyridine N-oxide belongs to an important class of heteroaromatic motif with unique reactivity pattern. In particular, the C-H bond at C-2 position of the pyridine N-oxide has been exploited for the introduction of various groups by C-H activation based coupling. Fagnou installed an aryl unit at the C-2 of pyridine N-oxide to obtain heterobiaryl N-oxide using aryl bromide and palladium catalyst.[7a] Subsequently, several sp^2-sp^2 based coupling partners such as aryl halides, triflate, boronic acid and electron poor alkenes were used to couple with pyridine N-oxide in the presence of various metal catalysts.[7] Coupling of heteroarene N-oxide with arene and heteroarene via an elegant dehydrogenative protocol has also been developed.[8] In this direction the coupling of the acyl fragment, generated from α-oxocarboxylic acid, to hetroarene N-oxide was conceived as shown in Table 1. It is noteworthy that the conventional procedure to synthesize C2-acylated pyridine N-oxide from ortho-acylated pyridine should be

[a] *Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai - 625 021, India.*
E-mail: muthumanian2001@yahoo.com
[b] *Syngene International Limited, Biocon, Bangalore - 560 099, India.*

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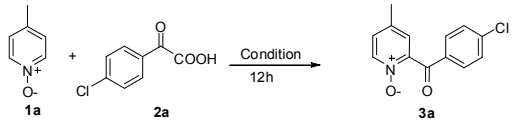
difficult due to the competitive Baeyer-Villiger oxidation involving the acyl group.

Table 1. Screening impact on reagents and solvents.



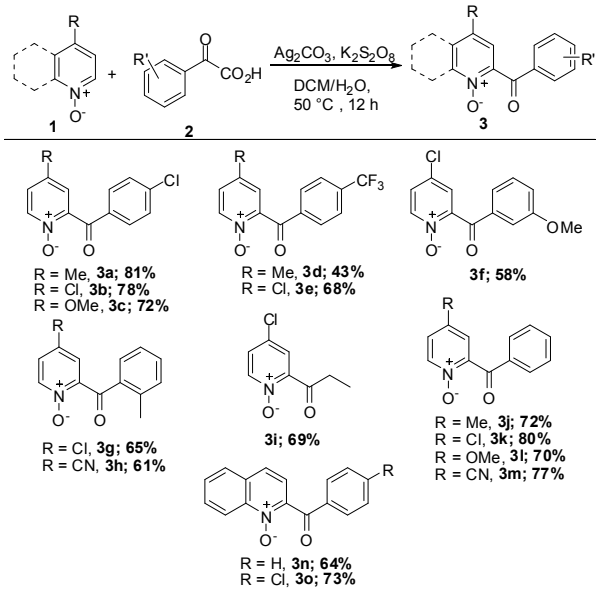
Entry	Catalyst (10 mol %)	Oxidant (2eq)	Solvent	Temp °C	Yield of **3a** (%)[a]
1	$Cu(OAc)_2$	TBHP	DMF	100	28
2	$Cu(OAc)_2$	Ag_2O	DMF	100	45
3	$CuSO_4.5H_2O$	TBHP	DMF	100	28
4	$CuSO_4.5H_2O$	$K_2S_2O_8$	DMF	100	32
5	$FeSO_4.7H_2O$	$K_2S_2O_8$	DCM/H_2O	50	40
6	$Pd(OAc)_2$	$K_2S_2O_8$	DMSO	80	38
7	$Mn(OAc)_3$	-	HOAc	80	25
8	-	CAN	CH_3CN	80	-
9	AgOAc	$K_2S_2O_8$	DCM/H_2O	50	22
10	$AgNO_3$	TBHP	DCM/H_2O	50	41
11	$AgNO_3$	$NH_4S_2O_8$	DCM/H_2O	50	53
12	$AgNO_3$	$K_2S_2O_8$	DCM/H_2O	50	59
13[b]	Ag_2CO_3	$K_2S_2O_8$	DCM/H_2O	50	65
14[c]	Ag_2CO_3	$K_2S_2O_8$	DCM/H_2O	50	81
15	Ag_2CO_3	O_2	DCM/H_2O	50	16
16	Ag_2CO_3	Oxone	DCM/H_2O	50	11

[a] Isolated yield. [b] Reaction condition: aryl-*N*-Oxide (0.46mmol), α- keto carboxylicacid (0.69 mmol),catalyst (10 mol%), oxidant (0.92 mmol) in DCM:water mixture (2 mL, 3:1), 50 °C, 12 h. [c] 0.92 mmol of acid and 1.38 mmol of oxidant used.

Normally the expensive palladium catalyst is used for the decarboxylative acylation.[9] Silver is relatively less expensive and various salts of silver are readily available. Carboxylic acids are prone for decarboxylation in presence of silver and thus this property has been harnessed to transform the carboxyl group to other useful functional groups. Halo derivatives can be obtained from the carboxylic acid by Hunsdiecker reaction through a radical process.[10] The use of silver catalyst towards carbon-carbon bond formation is relative scarce.[11] Though the role of silver in oxidative decarboxylation was recognized long back, its potential has not been extensively explored.[11f,g] In this communication, we disclose a silver catalyzed decarboxylative coupling of α-oxocarboxylic acid with pyridine *N*-oxide through a radical process.

Our study commenced by optimising the reaction between 4-methylpyridine N-oxide (**1a**, R = 4-Methyl) and 4-chlorophenylglyoxylic acid (**2a**, R = 4-Chloro) with different metal catalysts, oxidants and solvents (Table 1). Initial screening with 10 mol% copper acetate and 2 equiv. of TBHP in DMF gave **3a** in 28% yield. However with silver oxide, better result has been noticed. The yield of the reaction did not improve with copper sulphate, ferrous sulphate, $Mn(OAc)_2$ and $Pd(OAc)_2$. Treatment with CAN led to the decomposition of 4-chlorophenylglyoxylic acid. Silver nitrate with TBHP gave **3a** in 41% yield. Optimization with $(NH_4)_2S_2O_8$ and oxone didn't enhance the yield considerably. Performing the reaction with silver nitrate and $K_2S_2O_8$ resulted in good yield, whereas silver carbonate displayed the best yield at 50 °C. The mixture of dichloromethane and water was found to be the superior reaction medium. Having identified the suitable conditions, various heteroarene N-oxides **1** were subjected to acylation with various α-oxocarboxylic acids **2** (Table. 2). 4-Chlorophenylglyoxylic acid underwent acylation with substituted pyridine N-oxides and quinoline N-oxide.

Table 2 Decarboxylative acylation of various aryl-*N*-oxides



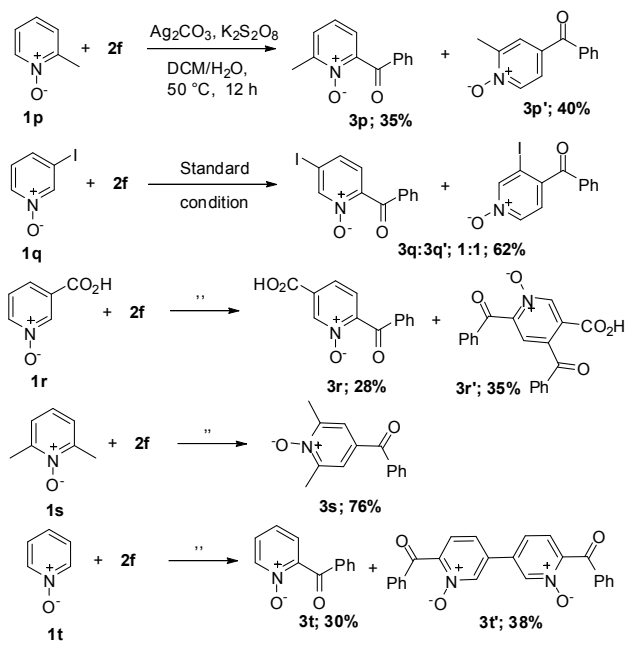
Reaction condition: **1** (0.46 mmol), **2** (0.92 mmol), catalyst (10 mol%), oxidant (1.38 mmol) in DCM:water mixture (2 mL, 3:1), 50°C, 12 h.

4-Trifluoromethylphenylglyoxylicacid and 4-methoxyphenylglyoxylic acid were successfully employed for the acylation emphasizing that the electronic factors is not influencing the reaction. Sterically hindered 2-methylphenylglyoxylic acid was also found to provide C2-acylation products. 2-Oxobutanoic acid, an aliphatic acid, was equally effective towards acylation. Coupling of phenylglyoxylic acid with various heteroarene *N*-oxides also worked well. With 4-chloropyridine *N*-oxide, the chloro group remained undisturbed during the acylation, though it could have undergone decarboxylative-aryl chloride type coupling.[3a]

It is interesting to note that 2-methylpyridine N-oxide behaved in a different manner, as it delivered C4-acylation product **3p'** along with the expected C2-acylation product **3p** in nearly equal amount (Scheme 1). The formation of **3p'** strongly suggests that the decarboxylative acylation may not involve C-H bond activation. Similarly, 3-iodopyridine N-oxide also followed the same trend providing an inseparable mixture of **3q** and **3q'** in 1:1 ratio. More interestingly, 3-carboxypyridine N-oxide yielded acylated product **3r** along with the diacylated product **3r'**. Subjecting **3r** to standard condition provided **3r'** confirming that

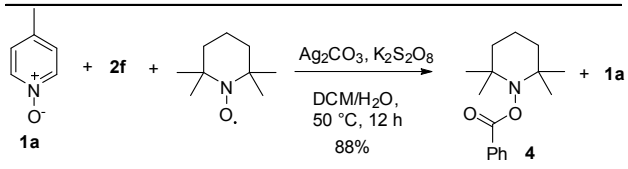
the latter would have been formed through a sequential acylation - first at C-2 and then at C-4. The carboxylic acid group in the pyridine *N*-oxide is survived in both the products, **3r** and **3r'**.[4i] The acylation has been effected on 2,6-dimethylpyridine *N*-oxide, the single product being the C4-acylated pyridine **3s**. These facts confirm that the decarboxylative acylation is taking place *via* a radical pathway.

Pyridine *N*-oxide without any substituent provided C2-acylated product **3t** and a coupled product **3t'**. The formation of **3t'** is more interesting and can be explained by considering a tandem process involving C2-acylation, dimerization at C5 followed by rearomatization to 3,3'-bipyridyl motif. 3,3'-Bipyridyl *N*-oxide can be easily converted to 3,3-bipyridyl, a well known ligand in the coupling reaction.



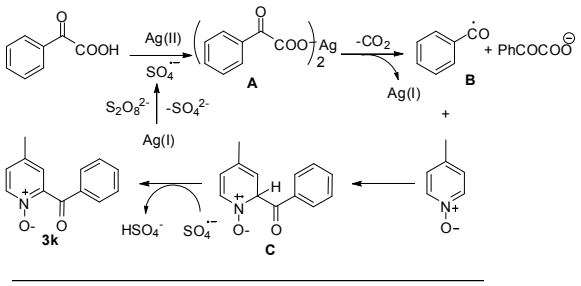
Scheme 1 Decarboxylative acylation of various aryl-N-oxides; Reaction condition: **1** (0.46 mmol), **2** (0.92 mmol), catalyst (10 mol%), oxidant (1.38 mmol) in DCM:water mixture (2 mL, 3:1), 50 °C, 12 h.

To ascertain the mechanism, the reaction was conducted in presence of radical scavenger TEMPO to inhibit the acylation as shown in Scheme 2. As anticipated, no acylated product was obtained in the reaction; only the adduct **4** was isolated which would have formed through the capture of acyl radical by TEMPO. Based on these results, a possible mechanism for the



Scheme 2 Attempted acylation in presence of TEMPO

acylation is proposed as shown in Scheme 3. Addition of the radical **B** with pyridine *N*-oxide generates another radical **C**. The sulphate radical anion helps in transforming the intermediate **C** to **3**.



Scheme 3 Possible mechanism for decarboxylative acylation

In summary, we described the acylation of pyridine *N*-oxide by α-oxocarboxylic acid in presence of silver catalyst. Acylated heterorene *N*-oxides, which are difficult to access by the conventional methods, can be synthesized successfully in high yield using this protocol. A range of functional groups tolerate the reaction condition. The reaction is found to follow a radical pathway.

Experimental Section

General procedure for the synthesis of 2 or 4-(substituted benzoyl)pyridine 1-oxide (3). The mixture of α-keto carboxylic acid **2** (0.92 mmol), substituted pyridine N-oxide **1** (0.46 mmol), silver carbonate (10 mol %) and $K_2S_2O_8$ (1.38 mmol) in DCM: H_2O (3:1, 2 mL) were stirred at 50 °C for 12 h. The reaction mixture was filtered through celite pad, washed with dichloromethane. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated in vacuum. Crude product was purified by flash column chromatography using 70-80 % ethylacetate in hexane mixture as the solvent to get derivative **3**.

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