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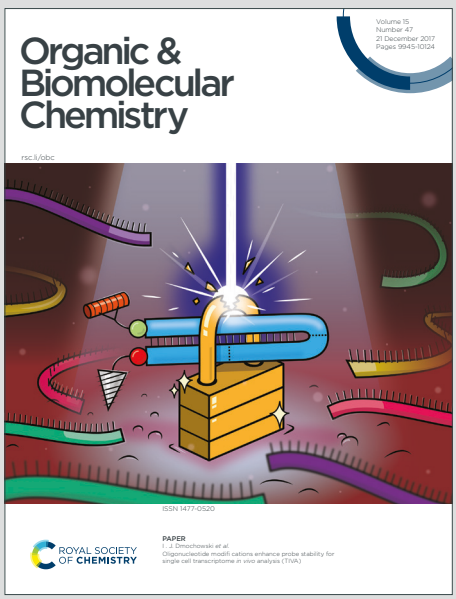

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COMMUNICATION

Access to pyrrolo[2,1-*a*]isoindolediones from oxime acetates and ninhydrin via Cu(I)-mediated domino annulations

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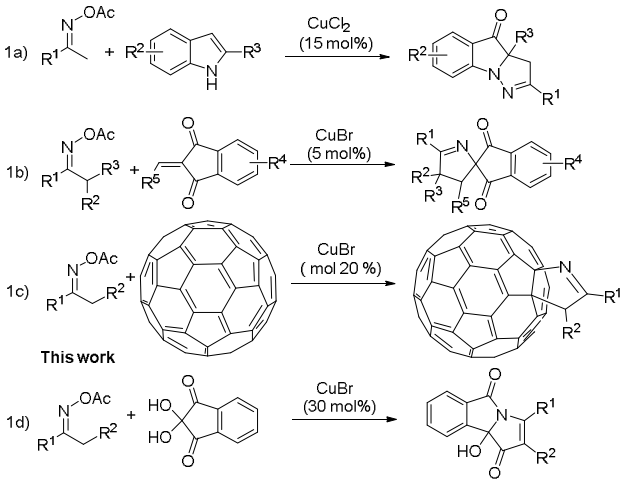
Atul Upare,[a,b] Neeraj Kumar Chouhan,[a,b] Andhavaram Ramaraju,[a] Balasubramanian Sridhar,[c] and Surendar Reddy Bathula*[a,b]

Abstract: A copper-mediated domino condensation reaction of readily accessible oxime acetates with ninhydrin is reported to afford pyrrolo[2,1-a]isoindolediones via new C-C & C-N bond formations. A wide range of oxime acetates were shown to generally participate in the reaction to produce the condensed products in excellent yields. The necessary control experiments were performed and mechanism is proposed to involve sequentially the formation of iminium radical via Cu-mediated N–O bond cleavage of oxime acetates, addition of the radical to ninhydrin and rearrangement via ring expansion.

Oxime *O*-ethers and esters are emerging as first-line synthons in modern heterocyclic chemistry because of their ready availability and easily activatable N-O bonds.[1-4] *O*-acetyl oximes can generate enamines in situ *via* copper-mediated N–O bond activation either by oxidative addition or by radical process.[5] The resultant enamines undergo [3+3] or [3+2]-type condensation reactions with suitable electrophiles such as aldehyde, malononitrile, β-ketoesters, carbonyl–amine condensates, alkenes, isothiocyanates and alkynes to produce six and five-membered N-heterocycles.[6] In this regard, several research groups have reported the utility of *O*-acyl oximes for the construction of a wide variety of N-heterocyclic compounds. For instance, Yoshikai *et al.* have reported the synthesis of pyridines from *O*-acyl oximes and α,β-unsaturated imines.[7] Jiang *et al.* have reported multiple methods for the synthesis of various N-heterocycles such as pyrrole, imidazo[1,2-a]pyridine, pyrazole, pyridine and 2-aminothiazole from *O*-acyl oxime and copper (I) catalysts.[8] Guan and co-worker have developed synthetic methods for symmetrical pyridines and pyrroles from *O*-acyl oxime using CuBr as catalyst.[9] Deng group have reported the construction of pyrazolo[1,5-*a*]indole derivatives from O-acyl oxime and indole (scheme 1a) via N1, C2, and C3 trifunctionalization of indoles in one-pot manner.[10] Wei group has synthesized spiropyrrolines from



Scheme 1. Copper-mediated synthesis of fused and spiro ring *via* oxime acetates.

O-acyl oximes and alkenes via Cu (I) catalyzed intermolecular cyclization reaction (scheme 1b).[11] Guan-Wu Wang has developed Cu(I)-catalyzed facile and efficient synthetic protocol for 1-fulleropyrrolines by heteroannulation of C60 with *O*-acyl oxime (scheme 1c).[12] Furthermore, our group has reported the synthesis of mono- and disubstituted pyrimidine and 4-functionalised quinolines from oxime acetates.[13] Along this line, further exploring the reactivity of *O*-acyl oximes, we herein report a copper-mediated [3+2] domino cyclization of oxime acetates and ninhydrin for the synthesis of novel 9b-hydroxy-1H-pyrrolo[2,1-*a*]isoindolediones (scheme 1d). Ninhydrin is a powerful electrophile having widespread application in organic and bio-organic sciences.[14]

We have initiated our study by investigating the Cu-mediated domino cyclization of acetophenone oxime acetate (**1a**, 1mmol) and ninhydrin (**2**, 1 mmol) in DMSO at 80 °C. We were pleased to find that the 9b-hydroxy-3-phenyl-1H-pyrrolo[2,1-*a*]isoindole-1,5(9bH)-dione **3a** was obtained in 20% yield in the presence of 10 mol% of CuI in open air (Table 1, entry 1). To our delight, increase in catalyst loading to 30 mol%

[a] Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India E-mail: bsreddy@iict.res.in http://www.iictindia.org/staffprofiles/staffprofile.aspx?qry=1836
[b] AcSIR (Academy of Scientific & Innovative Research), Ghaziabad, 201 002, India
[c] X-ray Crystallography Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India

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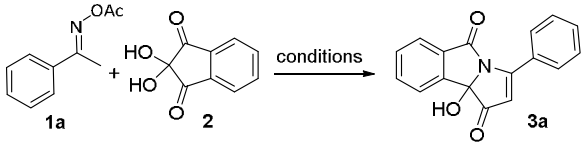
could enhance the yield of **3a** to 35% (entry 2). Further increase in catalyst loading up to 100 mol% did not show any improvement in the yield (entry 3). Encouraged by this result, we have increased the reaction temperature to 100 °C and **3a** was formed in 50 % yield. Further increase in the reaction temperature did not show any significant effect on the product yield (entry 5). Next, various copper catalysts, such as CuCl, CuBr, $CuCl_2$, $CuBr_2$ and $Cu(OAc)_2$, were screened to find out the effect of copper salts on the reaction efficiency (entries 6-10). CuBr was found to be the highest efficacious catalyst for the conversion, producing the desired 9b-hydroxy-3-phenyl-1H-pyrrolo[2,1-*a*]isoindole-1,5(9bH)-dione **3a** in 80% yield (entry 7). Moreover, changing the solvent to DMF was less efficient (entry 11) and no product formation was observed in 1,4-dioxane, toluene and THF (entry 12-14). In control experiment no product formation was observed in the absence of catalyst (entry 15).

Table 1. Optimisation of the reaction conditions.[a]

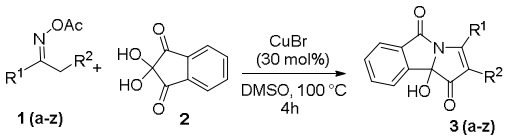


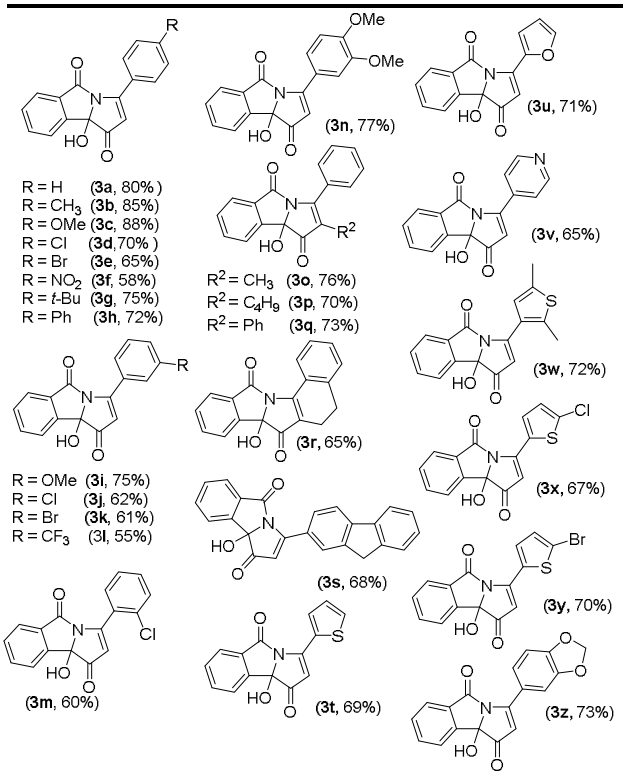
Entry	Catalyst (%Mol)	Temp (°C)	Solvent	Yield (%)
1	CuI(10)	80	DMSO	20
2	CuI(30)	80	DMSO	35
3	CuI(100)	80	DMSO	38
4	CuI(30)	100	DMSO	50
5	CuI(30)	120	DMSO	51
6	CuCl(30)	100	DMSO	65
7	**CuBr(30)**	**100**	**DMSO**	**80**
8	$CuCl_2$(30)	100	DMSO	N.R.
9	$CuBr_2$(30)	100	DMSO	N.R.
10	$Cu(OAc)_2$(30)	100	DMSO	N.R.
11	CuBr(30)	100	DMF	45
12	CuBr(30)	100	1,4-dioxane	N.R.
13	CuBr(30)	100	toluene	N.R.
14	CuBr(30)	100	THF	N.R.
15	--	100	DMSO	TRACE

[a] Reaction conditions: **1a** (1 mmol), **2** (1 mmol),catalyst (30 mol%), heated in DMSO (3 mL), at 100 °C for 4h. (N.R. = not reacted)

Having optimized reaction conditions in hand (table 1,entry 7), we subsequently examined the scope of this transformation with the broad range of ketoxime acetates and result are summarised in Table 2. This reaction exhibited good functional group tolerance and demonstrated to be a practical method for the synthesis of various pyrrolo[2,1-*a*]isoindolediones. Under the standard reaction conditions *para*-methyl, methoxy, chloro, bromo, nitro, t-butyl and phenyl substituted acetophenone oxime acetate produced corresponding pyrrolo[2,1-*a*] isoindoledione **3b**-**3h** in moderate to good yields (58-88%). Also, *meta*-methoxy, chloro, bromo and trifluromethyl substituted acetophenone oxime acetates successfully gave corresponding pyrrolo[2,1-*a*]isoindoledione **3i**-**3l** with 55-75% yield. In addition, *ortho*-chloro acetophenone oxime acetate also underwent the desired transformation to give the corresponding pyrrolo[2,1-*a*]isoindoledione **3m** in 60 % yield. Furthermore, 3,4 dimethoxy acetophenone oxime acetate **1n** proceeded smoothly to give the desired product **3n** 77% yield. These results indicate that the electronic (except nitro and triflurometh yl groups) as well as steric factors are not significantly affecting the conversion. Inspired by these results we have tested the fate of 2-substituted acetophenone oxime acetates under the standard reaction conditions. Propiophenone, hexanophenone and 2-phenylacetophenone oxime acetates (**1o**-**1q**) underwent the desired conversion to produce the corresponding 2-substituted Pyrrolo[2,1-*a*] Isoindolediones **3o** (76%), **3p** (70%) and **3q** (73%) in good yields. Moreover, α-tetralone and 2-acetylfluorene oxime acetates were tolerated in the reaction and afforded the corresponding products **3r** and **3s** in 65 and 68% yield.

Table 2. Synthesis of various pyrrolo[2,1-*a*]isoindolediones from aromatic oxime acetate.[a]





[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol),CuBr (30 mol%), heated in DMSO (3 mL), at 100 °C for 4h.

Next, a series of heteroaromatic ketoxime acetates (**1t**-**1y**) were investigated to extend the substrate scope. To our delight, thiophene, furan, and pyridine heterocycle based

ketoxime acetates reacted smoothly to give the desired product **3t**-**3v** in 65-71% yield. Moreover, substituted thiophene oxime acetate such as 2,5 dimethyl, chloro, bromo also reacted smoothly under standard conditions to give the desired product **3w**-**3y** in 67-72% yield. Finally, 3,4-methylenedioxyacetophenone oxime acetate also gave the corresponding product **3z** in 73% yield.

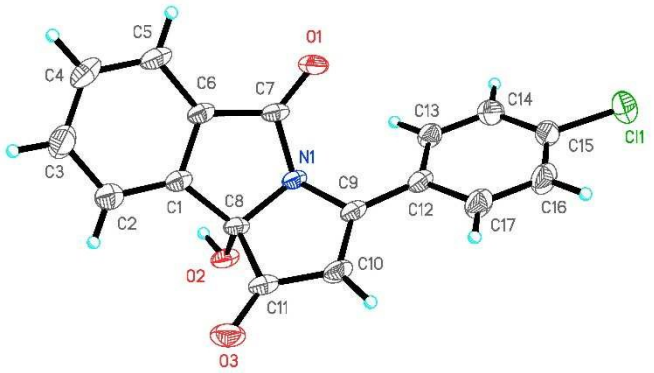
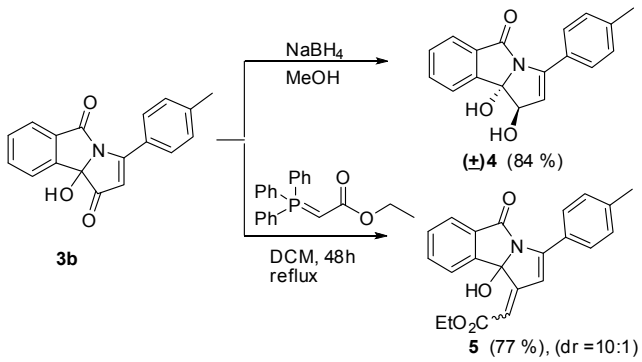


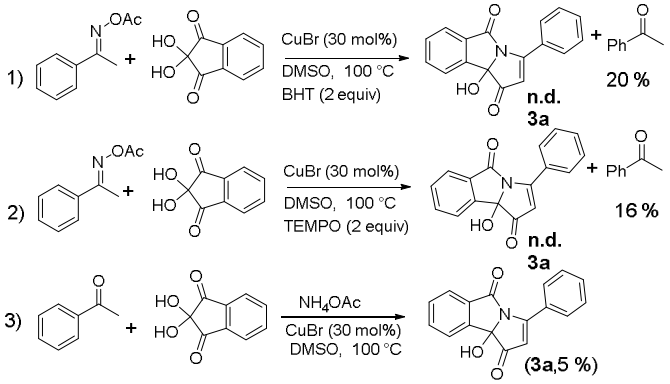
Figure 1. Structure of compound **3d** (CCDC 1954828) was confirmed by single crystal X-ray diffraction analysis.

Scheme 2: synthetic utility



To expand the synthetic utility of our developed protocol, we performed reactions using 3b as the starting materials to create diverse analogues of the title compounds (Scheme 2). We first reduced the keto group of 3b with $NaBH_4$ in a chemoselective manner. Surprisingly the reduction afforded the product **4** as a single isomer in 84% yield. The hydroxy chelated borohydride might have reduced it in an anti fashion to give the trans isomer selectively. However, we are unable to prove the structure unambiguously as we could not take the assistance of NOSY as there is no appropriate adjacent proton available. Further, we were able to perform Wittig reaction on the keto group of **3b** using ethyl (triphenylphosphoranylidene)acetate to obtain **5** with 10:1 dr in 77% yield. Conjugation and the probable hydrogen bonding between OH and COOEt might have afforded the stable trans product (Z-) as the major isomer.

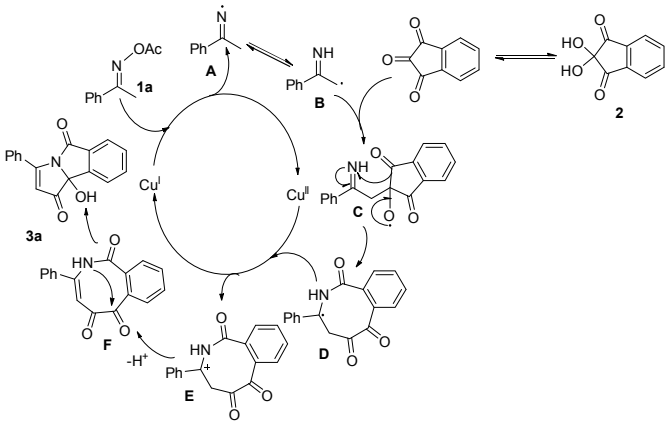
To understand the reaction mechanism some control experiments were conducted as shown in Scheme 3. Initially, we conducted a reaction in the presence of BHT to rule out any radical mediation (Scheme 3, eq. 1). When BHT was added to the reaction no product formation was observed, but 28% starting material was recovered and 20% acetophenone was also



Scheme 3: Control experiments. (n.d.= not detected)

isolated. Similar results were obtained with another radical scavenger TEMPO (eq. 2). These results indicate that the reaction proceeded through a radical pathway. Furthermore, replacement of acetophenone oxime acetate with acetophenone and ammonium acetate under the standard reaction condition (eq. 3) failed to produce the desired product, indicating the importance of oxime acetate.

On the basis of the above result and previous studies [8,9,11] a possible mechanism for this transformation is proposed in Scheme 4. Initially, N-O bond of *O*-acyl oximes was activated by Cu(I) *via* single-electron-transfer reaction to produce iminium radical **A**, which rapidly isomerised to carbon radical intermediate **B**.[8,11] Addition of intermediate **B** with ninhydrin constructed a new C–C bond to afford intermediate **C**. This oxy radical must have prompted the C-C bond cleavage to give strain free acyl radical which might have reacted on imine N towards stable benzyl radical intermediate **D**.[8f] Subsequently, the intermediate **D** was oxidised by Cu(II) to afford intermediate **E** with the regeneration of Cu(I).[8a,8e] After the expulsion of H^+, intermediate **E** was then transformed to intermediate **F** which cyclized to the desired product **3a** through a hemiaminal formation.



Scheme 4: Possible reaction mechanism.

In conclusion, a copper-mediated annulation reaction of readily accessible oxime acetates with ninhydrin is reported to give pyrrolo[2,1-*a*]isoindolediones via an N-O bond cleavage and C-C & C-N bond formations. The necessary control experiments were performed to establish the mechanism. A wide range of oxime acetates were shown to generally participate in the reaction to produce the condensed products in excellent yields.

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Conflicts of interest

There are no conflicts to declare.

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