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Authors: Krishna Pillai Kaliappan and Trisha Banik

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RESEARCH ARTICLE

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A Serendipitous One-Pot Cyanation/Hydrolysis/Enamide Formation: Direct Access to 3-methyleneisoindolin-1-ones

Trisha Banik,[a] and Krishna P. Kaliappan*[a]

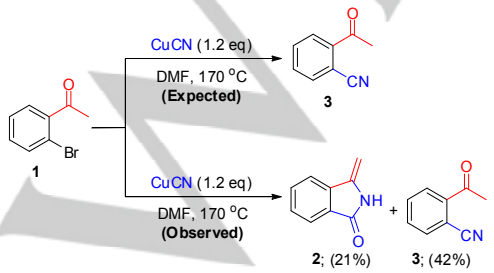
[a] Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai-400076

Abstract: A direct, one pot conversion of 2'-haloacetophenones to 3-methyleneisoindolin-1-one scaffolds using CuCN as the sole reagent without the need for moisture-free or anaerobic conditions is reported. This serendipitously discovered transformation with a broad substrate scope provides a significantly different route towards these important scaffolds. The scope of the method has also been further extended towards the synthesis of three special scaffolds, which are analogous to various bio-active drugs.

Introduction

The development of efficient synthetic methods for the formation of heterocyclic rings is one of the most extensively studied research areas in organic chemistry.[1] Among the various methods for the synthesis of heterocycles, one-pot reactions continue to attract synthetic community due to its potential in assembling complex molecular architectures quickly.[2] These transformations contribute towards implementing step economy and atom economy to complex processes, which are considered to be major criteria for a reaction to be efficient.[3] Owing to the fact that most of the biologically important molecules contain a variety of heterocyclic scaffolds, it is important to continue to develop newer methods towards the synthesis of novel scaffolds.

During the course of one of the ongoing projects in our laboratory,[4] we were in need of several 2'-acetyl substituted benzonitriles. While preparing this from 2'-bromoacetophenone **(1)** and CuCN under standard conditions for cyanation, to our surprise, in addition to the desired product **3** in 42% yield, a new compound, identified as 3-methyleneisoindolin-1-one **(2)**, after NMR and HRMS analysis, was obtained in substantial quantity (Scheme 1). Once the new compound was identified and fully characterized, it was deduced that cyanation, followed by unexpected hydrolysis of the resulting nitrile and subsequent enamide formation could have possibly produced this unexpected scaffold. It was also postulated that the hydrolysis had probably been facilitated by the presence of Cu(I) and trace amounts of moisture in commercial grade DMF, which was used for the reaction.



Scheme 1: Serendipitous formation of 3-methyleneisoindolin-1-one

With this serendipitous observation, an exhaustive literature survey indicated that a direct one-pot transformation from 2'-bromoacetophenones to 3-methyleneisoindolin-1-ones was indeed a useful transformation and holds immense potential. It was realized that among heterocyclic scaffolds, isoindolin-1-one ring systems are privileged units with applications in medicinal chemistry in the form of homo-*N*-nucleoside derivatives to assist in DNA recognition studies.[5] Isoindolinone on dimerization forms isoindigo, whose derivatives have been utilized as high performance polymers showing excellent photo-physical and electrochemical properties.[6]

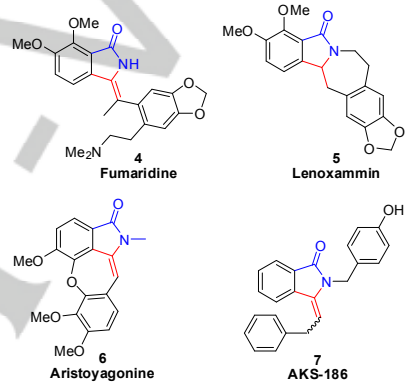
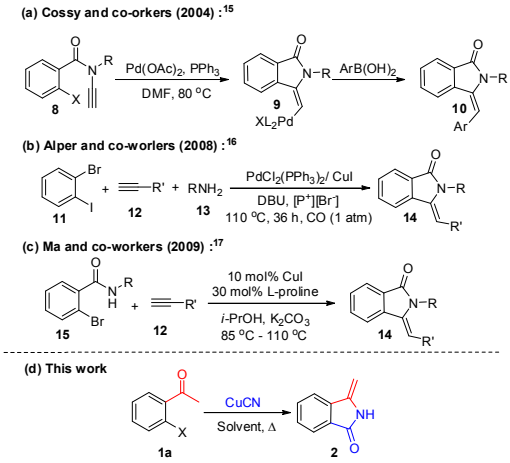


Figure 1: Pharmaceutically relevant compounds

The 3-methyleneisoindolin-1-one moiety also exists in natural products like aristolactams and piperolactams, which exhibit inhibitory activities against platelet aggregation induced by collagen and arachidonic acid (Figure 1).[7] Apart from these, a variety of other biologically active natural products contain a 3-methyleneisoindolinone scaffold and owing to this, several protocols for the synthesis of this class of compounds have been developed.[8]

The earlier methods for the construction of this unique class of heterocyclic moieties include the Horner–Wadsworth–Emmons type of condensation,[9] photolytic or electrolytic addition and condensation of phthalimides,[10] 5-*exo*-dig cyclization of pre-formed *o*-(alkynyl)benzamides through electrophilic activation of triple bonds.[11] Base triggered direct nucleophilic attacks on *o*-substituted triple bonds by amides[12] or nitriles[13] have also been explored. In 2013, Kobayashi and co-workers synthesized 2,3-dihydro-3-methylidene-1*H*-isoindol-1-ones, by the reaction of 2-formylbenzonitriles with dimethyloxosulfoniummethylide, generated from trimethylsulfoxonium iodide and NaH.[14] However, these methods have been either associated with poor regioselectivity in case of unsymmetrical substrates or required a number of additional synthetic steps. In order to overcome these drawbacks, various groups resorted to using transition metal catalyzed reactions such as Heck–Suzuki–Miyaura

domino sequences involving ynamides [Scheme 2(a)],[15] Sonogashira coupling-carbonylation–hydroamination of *ortho*-dihaloarenes [Scheme 2(b)][12b,16] and domino coupling-hydroamination of *ortho*-halobenzamides (Scheme 2(c)).[17]



Scheme 2: Reported methods for synthesis of 3-methyleneisoindolin-1-one scaffolds

Later in 2014, the groups of Lee[18a] and Patel[18b] utilized alkynyl carboxylic acids to synthesize 3-methyleneisoindolin-1-one derivatives *via* decarboxylative coupling with nitrogen donors. Perhaps the most widely used tool for the synthesis of this scaffold has been directing group assisted C-H activation,[19,20] though most of these methods employ the use of expensive transition metals, coupled with stoichiometric amounts of metal based oxidants and highly activated olefinic reactants like acrylates,[19a-h] vinyl sulfones,[19h,i] styrenes,[19j,k] difluoroalkenes,[19l] or even alkynes.[20] Although these one-pot routes are attractive methods to construct this scaffold of interest, they either require a multistep preparation of the starting materials or involve multi component transformations, which often tend to suffer from the formation of side products.

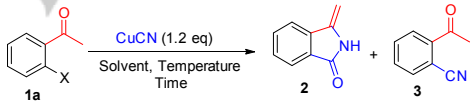
Thus in order to address these limitations, and in line with our long-standing interest in the synthesis of various biologically important heterocyclic scaffolds[21], we sought to pursue this serendipitously discovered one-pot transformation towards the synthesis of 3-methyleneisoindolin-1-ones [Scheme 2(d)]. We realized that efficient optimization of this transformation using operationally simple conditions could provide a highly useful synthetic methodology.

Results and Discussion

Having already observed the product formation with commercially available LR-grade DMF (Table 1, Entry 1), it was important to confirm whether the trace amounts of moisture was indeed driving the product formation. To this end, 2'-bromoacetophenone was chosen as the test substrate for optimization and it was reacted with CuCN in dry DMF (Entry 2). The formation of 2-acetylbenzonitrile **3** as the sole product was a clear indication that this is indeed the intermediate in this transformation, possibly formed by a Rosenmund-von Braun type cyanation on the aromatic halide.[22] However, the lack of formation of 3-methyleneisoindolin-1-one confirmed the requirement of moisture in the medium for hydrolysis and subsequent enamide formation.

So, in order to facilitate the hydrolysis of the intermediate nitrile **3**, water and acetic acid were added as additives, which marginally increased the yield (Entries 3, 4). The use of non-polar solvent toluene and polar aprotic solvent DMSO didn't give either of the products. However, NMP gave a mixutre of **2** and **3** in only moderate yield. On the other hand, switching to polar protic solvents like MeOH and *t*-BuOH at 80 °C, only the nitrile intermediate **3** was obtained with 43% and 39% yields respectively (Entries 8, 9). Nonetheless, when *i*-PrOH was used at 80 °C, significant amount of the product **2** was formed along with **3** and some unreacted starting material. Improved conversion of the nitrile into **2** was observed upon further heating up to 120 °C to afford 82% of the cyclized product (Entry 10). In order to reduce the reaction time, combination of solvents was then attempted. When a mixture of DMF and *i*-PrOH was used, the yield of the cyclized product was dropped to 43%, while the use of DMF and *t*-BuOH gave only **2** exclusively in 78% yield (Entry 12). The yield was further improved to 92%, when water was used as a co-solvent (Entry 13).

Table 1. Optimization[a]



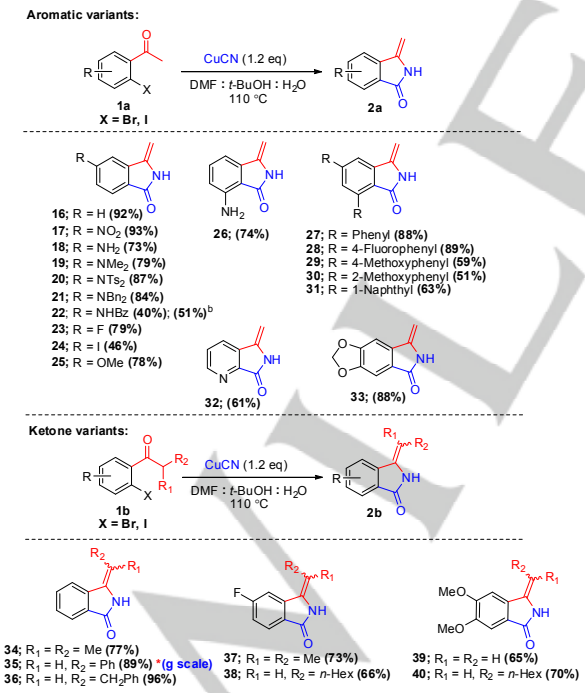
Entry	Solvent	Temp. (°C)	Time (h)	Yield (2)	Yield (3)
1.	DMF	170	24	21%	42%
2.	DMF (dry)	130	48	-	56%
3.[b]	DMF	150	6	59%	-
4.[c]	DMF	150	24	37%	-
5.[b]	Toluene	110	24	-	-
6.[b]	NMP	120	24	24%	31%
7.[b]	DMSO	110	6	-	-
8.[b]	MeOH	80	48	-	39%
9.[b]	*t*-BuOH	80	12	-	43%
10.[b]	*i*-PrOH	120	48	82%	Traces
11.[b]	DMF:*i*-PrOH (1:1)	110	24	43%	25%
12.[b]	DMF:*t*-BuOH (1:1)	110	24	75%	Traces
13.	**DMF:*t*-BuOH:H_2O (3:3:2)**	**110**	**20**	**92%**	**-**
14.[d]	DMF:*t*-BuOH:H_2O (3:3:2)	110	24	78%	18%
15.[e]	DMF:*t*-BuOH:H_2O (3:3:2)	110	18	54%	36%

a: X = Br, unless otherwise mentioned; all yields represent isolated yields; b: 1 drop of H_2O was added as additive; c: Acetic acid was added as additive; d: X = I; e:TBAI (cat. amount)

Among the aromatic halides, it was observed that bromides (Entry 13) produced better yield than iodides (Entry 14), while the use of a catalytic amount of TBAI with 2'-bromoacetophenone only decreased the yield of the product (Entry 15). So, the aromatic bromides were identified as the best starting materials for exploring the substrate scope of our transformation, except for a few substrates, where the iodinated compounds were more easily accessible.

With the optimized reaction condition in hand (Table 1, Entry 13), the substrate scope of this domino transformation was examined next. Very good functional group tolerance was observed at each end of the electronic spectrum. To our delight, both $-NO_2$ **(17)** and $-NMe_2$ **(19)** substituents furnished the corresponding products in very good yields. Free amine groups ($-NH_2$), which generally hinder transition metal mediated reactions, also worked efficiently under these reaction conditions **(18, 26)**. Amines derivatized as *bis*(sulfonamide) **(20)**, dibenzylamine **(21)** and benzanilide **(22)** also proved to be highly tolerant to the reaction conditions. Surprisingly, the *N*,*N*-dibenzoyl derivative upon treatment under the standard reaction conditions, provided the monobenzoyl derivative **(22)** (See Supporting Information). It may be reasoned that the one oft he benzoyl groups was hydrolyzed under the reaction condition. The presence of an extra fluoride on the aromatic ring was well tolerated **(23, 37, 38)**.

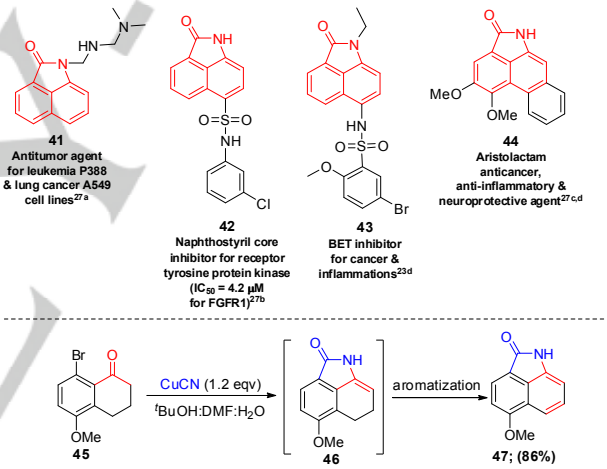
Scheme 3: Substrate scope[a]



a: All yields represent isolated yields; b: Obtained starting from *N*,*N*-dibenzoylated compound (see SI)

Disubstituted aromatic rings connected to the 2'-haloacetophenones also yielded very good results **(27-31)**. As a heteroaromatic variant, the reaction was attempted on a pyridine based scaffold to obtain a moderate yield (61%) of the cyclized product **32**. Finally when acetophenone derivatives were replaced with other ketones, the products containing substituted exocyclic double bonds were furnished in good to excellent yields **(34-40)**. It is worth mentioning that the formation of substrate **35** was achieved in 89% yield when the reaction was done at greater than 1 g scale. This further showcases the scalability of our transformation (Scheme 3).

Having successfully syntheiszed a variety of 3-methyleneisoindolin-1-ones, we looked at extending this methodology to synthesize another closely related class of compounds, benzo[*cd*]indol-2(1*H*)-ones, which are frequently found in a wide range of pharmaceuticals, dyes and natural products.[23] They also exhibit antitumor,[24] anti-inflammatory,[25] and antiplatelet activities.[26] Compounds **41**-**44** (Scheme 4) represent some members of this unique class of heterocycles, which show important biological activities.[23d,27]

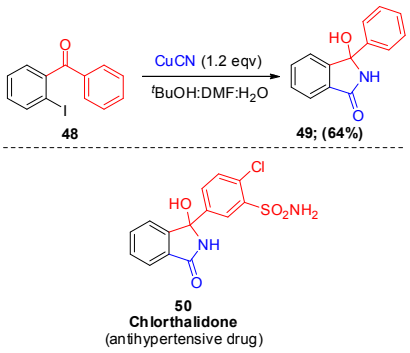


Scheme 4: Synthesis of benzo[*cd*]indol-2(1*H*)-one based drug analogue

However, synthetic routes to access this scaffold have often been inefficient and limited in scope. Traditionally, benzo[*cd*]indol-2(1*H*)-ones have been prepared from the reaction of 1,8-naphthalic anhydride with hydroxylamine hydrochloride employing very harsh conditions , while exhibiting a very narrow substrate scope.[23c,d, 27a,b, 28] However, there have been more recent methods which have managed to overcome these obvious shortcomings including base mediated benzannulation,[29] reductive cyclization,[30] aminocyclization on triple bonds,[31] and transition metal catalyzed carbonylative C-H activation.[32] To this end, we envisaged that our CuCN mediated transformation may be easily employed to address some of the drawbacks of the aforementioned methods in the synthesis of benzo[*cd*]indol-2(1*H*)-one derivatives. In order to probe the feasibility of this hypothesis, the tetralone **45** was treated under our standardised conditions to obtain the 3-methyleneisoindolinone intermediate **46**, wherein the newly

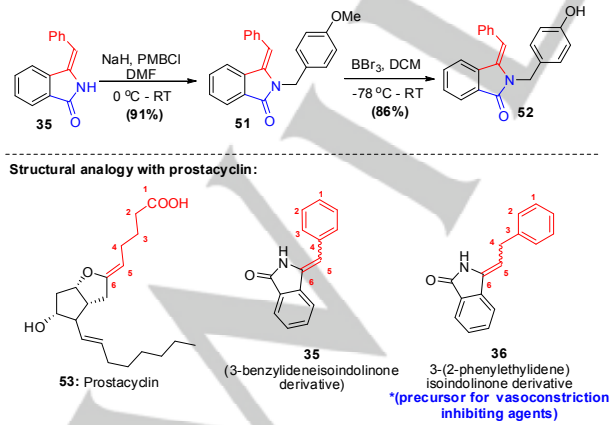
formed exocyclic double bond was part of the ring. Interestingly, this underwent concomitant aromatization to furnish benzo[*cd*]indol-2(1*H*)-one **47** in 86% yield, which illustrates the potential application of our methodology (Scheme 4).

When the benzophenone derivative **48** lacking an α-hydrogen on the ketone was reacted, the corresponding aminol **49** was obtained. Interestingly, this aminol was a direct analogue of chlorthalidone **(50)**, which is very commonly used as an anti-hypertensive drug[33] (Scheme 5).



Scheme 5: Synthesis of chlorthalidone analogue

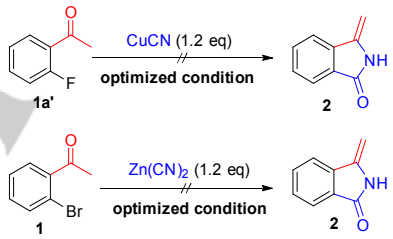
Among the 3-methyleneisoindolin-1-one based compounds in Figure 1, a lot of synthetic as well as biological studies have been devoted towards AKS-186 **(7)**. AKS-186, belonging to the family of 3-(2-phenylethylidene)isoindolinone compounds **(36)**, is known to inhibit U-46619-induced vasoconstriction of pig coronary artery with an impressive IC_{50} value of 0.6 μM.[34] In this regard, the compound **36** is a direct precursor for AKS-186 as well as other derivatives of the same, each of which have impressive biological profiles. Structure-activity relationship studies on this class of pharmaceutically important compounds have indicated that the one carbon lower analogues of AKS-186 **(35)** also show inhibitory activity towards the type of vasoconstriction mentioned above, albeit to a lesser extent.



Scheme 6: Synthesis of one carbon lower analogue of AKS-186

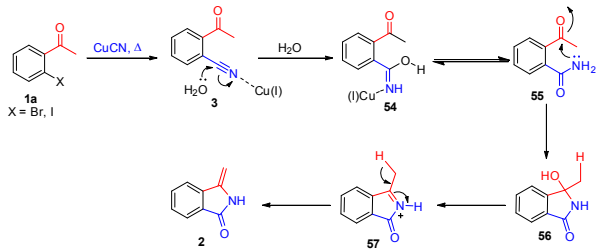
As a matter of further interest, the exocyclic olefin in this class of compounds have also been considered equivalent to the 5,6-double bond of prostacyclin (PGI_2) (Scheme 6).[35] In order to further extend our current methodology, we wanted to synthesize the 3-benzylideneisoindolinone analogue **(52)** of AKS-186.To this end, the free N-H of the substrate **35** was converted to its corresponding PMB-derivative. Upon subsequent treatment with BBr_3, demethylation was achieved to obtain the lower analogue of AKS-186 **(52)** in 86% yield (Scheme 6). SAR studies on 3-methyleneisoindolinones have led to the conclusion that the geometry of the exocyclic double bond has little bearing on the biological activity of the compounds.[34]

In order to probe further into the mechanism of this unexpected transformation, a couple of experiments were carried out. Treatment of 2'-fluoroacetophenone **(1a')** under the standard reaction conditions left the starting material untouched. This suggested that the mechanism for cyanation might not be S_NAr type, thereby indicating a Rosenmund-von Braun type cyanation process. In order to further establish this idea, an alternative cyanide source like $Zn(CN)_2$ was used, which too, failed to react with 2'-bromoacetophenone. This further confirmed that CuCN was indispensible for our purpose and Cu was probably playing a key role in the cyanation process (Scheme 7).



Scheme 7: Mechanistic studies

The observation of the formation of 2-acetylbenzonitrile **(3)** was a strong indication that the mechanism for this one-pot transformation proceeds initially *via* a Rosenmund-von Braun type cyanation in the presence of CuCN at high temperatures, followed by Cu-assisted concomitant hydrolysis of the nitrile to the amide **55**.[36] Subsequently, the amide nitrogen undergoes a 5-*exo*-trig cyclization with the ketone to generate the aminol **56**, which dehydrates to form the transient iminium ion **57**. Finally the iminium ion undergoes deprotonation to form our desired 3-methyleneisoindolin-1-one **(2)** to complete the transformation. (Scheme 8).



Scheme 8: Probable mechanism for the one-pot transformation

Isolation of the substrate **49** (as shown in Scheme 5) was conclusive evidence for an aminol intermediacy in our transformation.

Conclusion

In summary, we herein report a serendipitous obervation of an one-pot transformation of 2'-haloacetophenones to 3-methyleneisoindolin-1-ones, an important class of heterocycles. This reaction was carefully optimized further to synthesize a wide range of derivatives in good to excellent yields, exhibiting good scalability under a set of simple reaction conditions. This method has also been successfully extrapolated towards the synthesis of three drug analogues, including the one carbon lower analogue of AKS-186, which is a well known vasoconstriction inhibitor. The fact that moisture-free or anaerobic conditions are not necessary and only CuCN is enough to achieve this transformation makes it one of the efficient methods for the construction of these biologically important scaffolds.

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Keywords: 3-methyleneisoindolin-1-one • Heterocycles • Cyanation • Enamide formation • One-pot transformation

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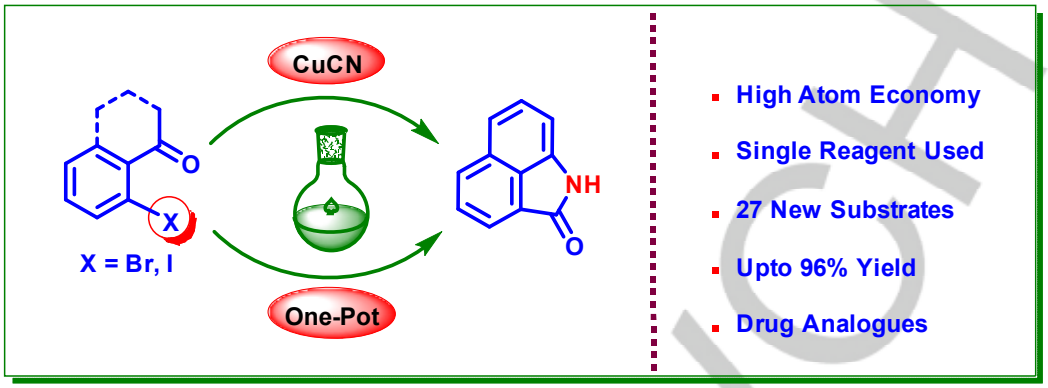

CuCN does it alone: A direct one-pot transformation of 2'haloacetophenones to 3-methyleneisoindolin-1-ones has been described. CuCN mediates the 4-step transformation under highly robust conditions, accompanied by high yields and efficient atom economy.