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Beyond conventional routes, an unprecedented Metal-Free Chemoselective Synthesis of Anthranilate Esters *via* Multicomponent Reaction (MCR) Strategy

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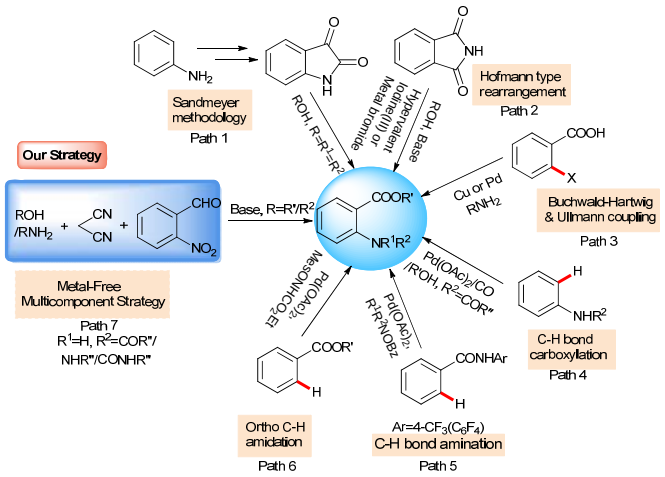
A hitherto unreported route for the synthesis of anthranilate esters is demonstrated using 2-nitrobenzaldehyde, malonitrile and alcohol or amine *via* metal and oxidant free multicomponent reaction (MCR) strategy. This process simultaneously installs an ester and urea or urethane functionality *via* a C–O and C–N bond formation *via* concurrent oxidation of the aldehyde group and reduction of the nitro group involving an intramolecular redox process.

Multicomponent reactions (MCRs)[1] have achieved a significant benchmark as they can give a direct access to unexplored territories of chemical entities or discover unique routes for the synthesis of structurally complex scaffolds using a single operation in a highly atom and step economic manner. Attaining the desired chemoselectivity in such strategies certainly provides additional flavors.[2] Moreover, when these distinct processes are blended with an intramolecular redox chemistry, the essence of such reactions amplifies in many fold.[3]

Anthranilic acids have been extensively employed as useful key building blocks in a multitude of natural products *viz.* benzoxazinones, indoles, acridinones, saccharin and they exhibit a broad spectrum of biological activities in medicinal chemistry.[4] Ester derivatives of such anthranilic acids *viz. N*,*N*-dimethyl anthranilate (MDA), ethyl anthranilate (EA) and butyl anthranilate (BA) are used commercially in perfume industry as well as flavoring agent. They are also employed as insect repellents as these compounds target the same neurons that respond to DEET (*N*,*N*-Diethyl-*meta*-toluamide).[5] Recently Kain *et. al* reported these anthranilate esters as suitable substitution of DEET as they are less toxic as well as affordable. In this perspective tremendous efforts have been made from the very past for the synthesis of anthranilic acid derivatives through cheap and easy synthetic routes.

The classical recipe for the synthesis of substituted anthranilic acids is *via* reaction of isatins starting from anilines using the multistep Sandmeyer methodology (Scheme 1, Path 1).[6] Over the years, numerous synthetic strategies have been developed for the construction of anthranilic acid derivatives as follows: Hofmann type rearrangement of aromatic/aliphatic imides using hypervalent iodine (III) and metal bromide (Scheme 1, Path 2)[7] or Buchwald-Hartwig cross-coupling and Ullmann type[8] coupling reactions using *ortho*-halobenzoic acid with arylamines (Scheme 1, Path 3) or C–H functionalization reactions through Pd-catalyzed *N*-directed C–H carboxylation of anilides, *N*-arylureas and *N*-substituted anilines (Scheme 1, Path 4).[9] Very recently anthranilic esters are even synthesized using Pd-catalyzed *ortho* C–H amidation of *N*-aryl benzamides and benzoic acids using their nitrogen (*N*) and oxygen (*O*) donor atoms, respectively, (Path 5 and 6).[10,11] Unfortunately, all these methods discussed above mostly rely on the use of precious transition metals like Pd and require harsh conditions such as high reaction temperature, CO atmospheric condition or scope for the formation of side products and prolonged reaction time. Hence, a mild, cheap and metal-free synthetic route is necessary to overcome all these limitations. Herein we report an unprecedented synthesis of anthranilic acid derivatives using 2-nitrobenzaldehyde, malonitrile and alcohol or amine *via* a metal and oxidant free multicomponent strategy at room temperature.



Scheme 1. Various Routes for the Formation of Anthranilic Acid Derrivatives

Taking accounts of our earlier studies, the substrate-selective reactions of different carbonyl moieties with malononitriles and nucleophiles under basic environments have shown unique selectivity in every means. We have demonstrated the chemoselective synthesis of pyridine and dihydropyridine skeletons using aldehydes as carbonyl source with malononitrile varying the nucleophiles from cyclohexylamines to benzylamines.[12] Switching from aldehydes to ketones in the presence of malonitrile, highly substituted 1,6-naphthyridine moiety was also synthesized by our

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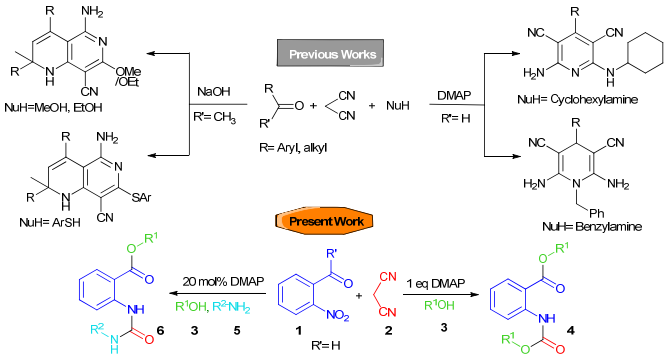


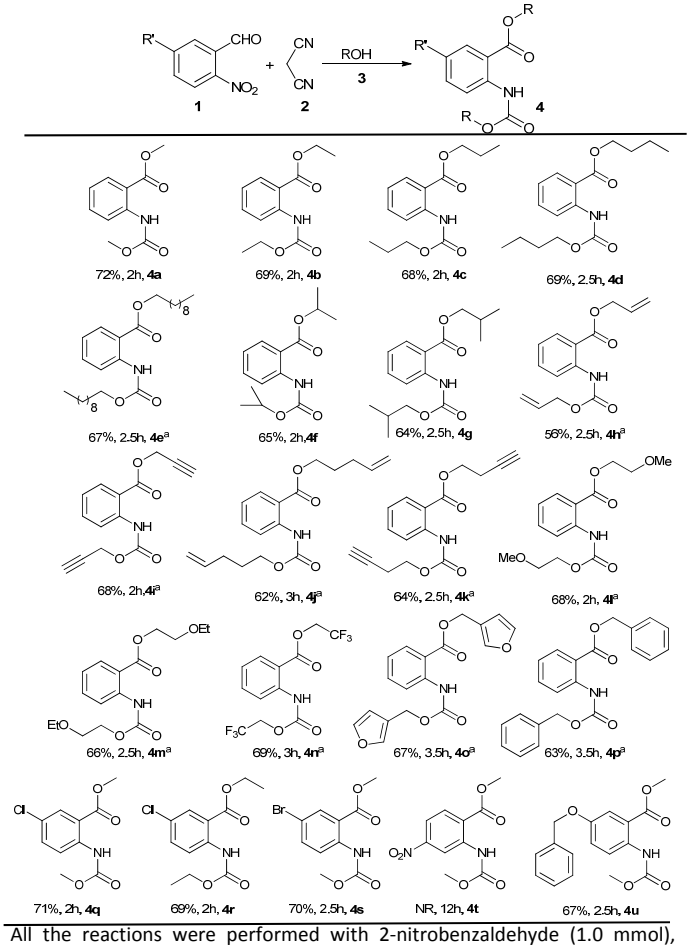
Scheme 2. Substrate Dependent Selectivity in Multicomponent Reaction

group using alcohol or thiol as the nucleophilic source.[13] In this context the use of 2-nitrobenzaldehyde instead of simple benzaldehyde as the carbonyl moiety in the presence of malonitrile and amine or alcohol as nucleophilic source provided anthranilate esters in an unprecedented way instead of anticipated pyridine or dihydropyridine skeletons. In this scenario, simultaneous installation of ester and urethane or urea functionality *via* a C–O and C–N bond formation through a chemoselective intramolecular redox process makes this metal and oxidant free strategy highly attractive and novel over the existing methods.

Buyout by this unusual result, an initial foray was intended using 2-nitrobenzaldehyde as the carbonyl source as well as malononitrile in MeOH using DMAP as the catalyst. After chromatographic purification, a white semi-solid product (**4a**) was isolated in 31% yield, which was characterized through spectroscopic analysis. In IR spectrum, it showed two characteristic strong absorptions at 1739 and 1692 cm^{-1} due to the carbonyl groups but the strong absorption around 2200 cm^{-1} for -CN group was found to be missing. Similarly, in the ^1H NMR spectrum **4a** exhibited two singlets at δ 3.91 and 3.78 due to –OMe groups and in the ^{13}C spectrum peaks at δ 168, 154 stated the presence of the carbonyl type skeleton. We would have expected the characteristic stretching frequency at 2240 cm^{-1} for the –CN group for the Knoevenagel product **A** and in ^1H NMR signals at δ 8.97 as a singlet for the Knovenegel proton. These observations indicate that the final product so obtained was methyl 2-(methoxycarbonylamino)benzoate (**4a**), an entirely different compound containing ester and urethane functionality along with two –OMe groups from reactant-cum-solvent MeOH.

To ascertain the optimized conditions, the same set of reactions was carried out using 0.5 equiv, 1 equiv and 1.5 equiv of DMAP (entries 1-3, Table SI-1, See Supporting Information) successively. It can be stated here that increasing the amount of DMAP from 0.5 equiv to 1 equiv effectively increased the yield from 54% to 72% (Table SI-1, entry 1-2). However, there was no effective improvement of yield when the amount of base was further increased upto 1.5 equiv (Table SI-1, entry 3). To examine the effectiveness of other bases, the reaction was screened not only with various other organic bases such as DBU, PPh_3, Et_3N, DMA but also with an inorganic base as NaOH (Table SI-1, entries 4-8). Unfortunately, DBU and PPh_3 exhibited poor reactivity compared to Et_3N and NaOH. To scrutinize the effect of solvent, the same reaction was carried out with various solvents using MeOH as reactant. It was observed that except for acetonitrile (Table SI-1, entry 9) other solvents led to lower yield or took prolonged reaction time (Table SI-1, entries 10-12). As CH_3CN showed competent efficacy as solvent it was concluded that this reaction can also be carried out commendably using alcohol as reactant. It is noteworthy to mention here that in the absence of any base only the

Table 1. Synthesis of product from various alcohol derivatives

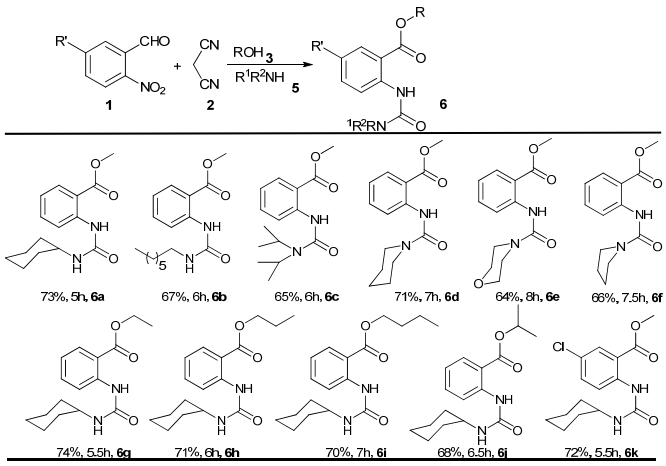


All the reactions were performed with 2-nitrobenzaldehyde (1.0 mmol), malononitrile (1.5 mmol) in presence of DMAP (1 equiv) in alcohol as solvent at rt. [a]Alcohol (2.0 mmol) used as reactant in CH_3CN solvent.

Knoevenagel product was obtained along with no traces of our desired anthranilate ester moiety (Table SI-1, entry 13).

With the optimized condition in our hand, the scope of this reaction was explored with various types of alcohol moieties. The reaction was performed with easily available homologous alcohols *viz.* methanol, ethanol, *n*-propanol and *n*-butanol (**3a**-**d**). Although the yield decreased from methanol to ethanol slightly, but further increase of the length of the straight-chain didn't affect the product yield. Even reactions with long chain such as *n*-decanol provided **4e** with moderate yields under optimized reaction conditions. Next the reaction was performed with alcohols such as isopropyl alcohol, a secondary alcohol and isobutyl alcohol to give desired esters **4f** & **4g** in good yields (See Table 1). Unfortunately, when the reaction was further performed with *t*-butanol, no product was formed due to the steric effect of the bulky tertiary butyl group. To observe the effect of sensitive functional groups present in the alcohol skeleton, we carried this reaction in the presence of allyl alcohol, propargyl alcohol, 4-pentene-1-ol and 3-butyene-1-ol (**3h**-**k**). All these reactions provided our desired product in 56-68% yields. Next, we wanted to see the influence of donating property in the alcohols. When the reaction was conducted with 2-methoxyethanol or 2-ethoxyethanol, good to moderate yields (**4l** & **4m**) were observed with the –OMe or –OEt group as substituents in ethanol. But the reaction did not proceed at all with 2-cyanoethanol may be due to the presence of the strongly electron withdrawing cyano (-CN) moiety. Contrary to this observation this reaction provided the

Table 2. Synthesis of product from various amine derivatives



All the reactions were performed with 2-nitrobenzaldehyde (1.0 mmol), malononitrile (1.5 mmol) and requisite amine (1.0 mmol) in presence of DMAP (20 mol %) as catalystat in alcohol as solvent at rt.

desired anthranilate ester **4n** when trifluoroethanol (CF_3CH_2OH) was used under the optimized reaction conditions. The use of heteroaromatic and aromatic alcohols such as furfurylalcohol (**3o**) and benzylalcohol (**3p**) also provided the desired anthranilate esters (**4o** & **4p**) with moderate yields. Next we have executed the reaction with substituted 2-nitrobenzaldehyde with MeOH and EtOH under standard conditions. Similarly, 5-chloro- and 5-bromo 2-nitrobenzaldehyde provided the anthranilate esters **4r-s** in good yields. Likewise, the substrate O-benzyl moiety in 2-nitrobenzaldehyde afforded the desired product **4u** with moderate yield. However, the reaction did not occur with the substrate 2,4-dinitrobenzaldehyde under identical conditions may be due to strong electron withdrawing nature of nitro group.

Encouraged by the above results, we wanted to extend the generality of this protocol in the presence of various aliphatic amines. Due to the more basic nature of such amines compared to alcohol, catalytic amounts of DMAP was used during the reaction. Thus reaction was conducted with primary amines such as cyclohexylamine and heptyl amine in methanol to give our desired product **6a**-**b** in good to moderate yields (See Table 2). The formation of unsymmetrical anthranilate esters by the addition of amine as well as alcoholic moiety in the skeleton rather than the symmetrical esters derived from both side alcoholic components was also a surprise to us.To extend the scope of this reaction, similar reactions were also performed with different secondary amines as diisopropyl amine, piperidine, morpholine and pyrrolidine (**5c**-**f**) under optimized reaction conditions which provided the desired products (**6c**-**f**) in fair yields. Further, we conducted this reaction with other easily available solvents such as EtOH, PrOH, BuOH in the presence of cyclohexylamine as the urea source to give anticipated products **6g** to **6i**, respectively. The yield didn't effect significantly with the growth in the length of the chain from MeOH to BuOH. The yield of the reaction further slightly decreased upto 68% (**6j**) while conducting this reaction in presence of isopropanol. Moreover, the reaction with the substrate 5-chloro-2-nitrobenzaldehyde provided the desired unsymmetrical anthranilate ester **6k** in good yield.

The structure of such anthranilate esters and alkyl 2-ureido-benzoate derivatives were unambiguously confirmed by the X-ray crystal structure analysis of **4n** & **6a**, which is shown in Figure 1.

In order to elucidate the possible mechanism for the reaction, a series of control experiments were carried out. The reaction was found to take place solely in the presence of malononitrile. When this reaction was conducted with ethyl cyanoacetate in lieu of malononitrile, methyl-2-aminobenzoate (**7a**) was formed (Scheme 3, Path 1). However, the reaction didn't proceed at all in the presence of diethyl malonate (Scheme 3, Path 2). Both these results demonstrate the inevitable role of the –CN groups in this reaction.

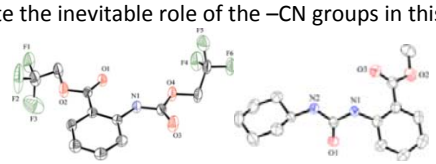
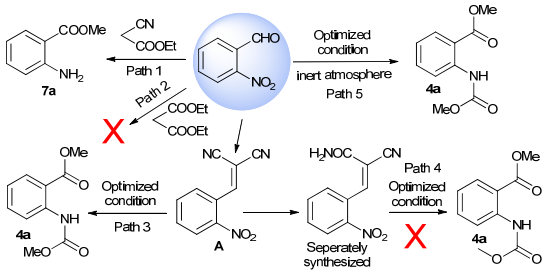


Figure 1: X-ray Crystal structure of **4n** (CCDC 1054296) & **6a** (CCDC 1060211) (see Supporting Information for further details)

Actual question arises whether it goes through an intramolecular or an intermolecular pathway. This specific redox reaction does not occur for benzaldehydes having the nitro group at *meta* or *para* position. A control reaction was carried out with 4-chlorobenzaldehyde, nitrobenzene under optimized conditions to see whether the reaction proceeds utilizing nitro group and aldehyde moieties from two different components *via* intermolecular fashion or not. Unfortunately, the reaction didn't proceed at all confirming that the reaction goes through an intramolecular pathway.

Separately synthesized Knoevenagel product **A** of corresponding 2-nitrobenzaldehyde and malononitrile provided our desired product (**4a**) under optimized reaction conditions (Scheme 3, Path 3).This signifies that the reaction is going *via* a Knoevenagel product **A**.



Scheme 3. Various control experiments during mechanistic study

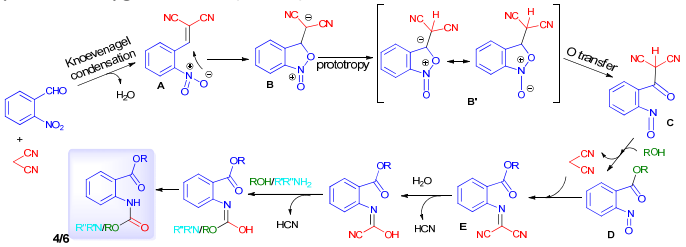
According to a literature survey a nitro group can directly react with an amine functionality to give -N=N- frameworks under basic environment.[14] However, in our case the reaction of presynthesized starting material 2-cyano-3-phenylacrylamide[15] was unsuccessful to provide the desired product under optimized reaction condition (Scheme 3, Path 4). This concludes that the –CN group is not reduced to the corresponding amide during the reaction.

Literature survey conveys the involvement of aerial oxygen during metal-free cyanation of α,β–unsaturated carbonyl compounds.[16] Keeping this observation in mind when our reaction was conducted under inert atmosphere, reaction proceeds with equal ease (Scheme 3, Path 5). This control experiment excludes the presence of aerial oxygen as the ester oxygen source.

To ascertain whether this reaction is going through a radical pathway or not, both 2,2,6,6-tetramethylpyridine-N-oxide (TEMPO) and azobisisobutyronitrile (AIBN) were employed as radical quencher and radical initiator respectively to note any influence over the reaction. However there was no substantial change in the product yield indicating the reaction may not be going through a radical pathway.

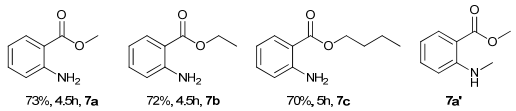
Although the exact mechanism is still unclear, taking into account of all the above observations a plausible mechanism for the formation of anthranilate esters (**4** & **6**) is depicted below. The first step is the condensation of malonitrile with the aldehyde group leading to the ß,ß-dicyanovinyl derivative **A**. Then Michael-type addition[17] of the

nitro group to the dicyanovinyl moiety takes place leading to the formation of five membered isoxazolium moiety **B**. In the next step prototropic tautomerism **B'** occurs and subsequent O-transfer to give the intermediate **C**. Alcoholysis of this compound **C** provides the 2-nitroso-benzoic acid ester **D** and malonitrile. The nitroso group further reacts with *in situ* generated malonitrile leading to a dicyanomethylidene imine **E** and one molecule of water. Hydrolysis with the water molecule followed by alcoholysis gives the product and two molecules of HCN. The explanation of the mechanism presumably dictates the delicate role of malononitrile throughout this intramolecular redox chemical process for the generation of this unexpected anthranilate esters.To confirm the possible oxygen source of urethane moiety the reaction of 2-nitrobenzaldehyde was conducted in the presence of 20 equiv of H_2O^{18} under otherwise identical condition. The anthranilate ester **4a** obtained herein contains slight amount of O^{18} incorporation indicating H_2O as the possible oxygen source (See SI).

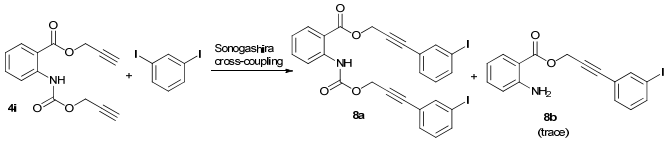


Scheme 4: Plausible mechanism for formation of anthranilate esters

As we have mentioned earlier, ester derivatives of such anthranilic acid *viz* methyl anthranilate (MA), ethyl anthranilate (EA), butyl anthranilate (BA) and dimethylanthranilate (MDA)are used widely as insect repellents.[4,5] They are even engaged commercially as flavoring agent or in perfume industry. In our above mentioned procedure we can directly synthesize MA, EA, BA (**7a**, **7b** & **7c**) from ethyl cyanoacetate (Scheme 3, Path-1). MDA (**7a'**) can synthesized through mono-*N*-methylation of MA **7a**.



It should be marked that the richness of the functionality in these anthranilate esters may render these compounds as beneficial synthons in further synthetic organic conversions. The compound **4i** containing alkyne functionality can be further used in Sonogashira Cross-coupling reactions with 1,3-di-iodobenzene.



Scheme 5: Application of **4i** in Sonogashira Cross-coupling

In summary, we have developed a convenient and novel route for the synthesis of anthranilate esters of potent synthetic and pharmacological importance *via* base assisted multicomponent reaction utilizing readily available 2-nitrobenzaldehyde, malonitrile and alcohols / aliphatic amines in a highly chemoselective manner. This strategy demonstrates a mild, cheap, metal-free chemoselective intramolecular redox process where simultaneously oxidation of the aldehyde functionality as well as reduction of nitro group takes place in the presence of malononitrile as the carbonyl source. By subtle change of the basic strength, a variety of symmetrical and unsymmetrical anthranilate esters can be efficiently synthesized in a highly chemoselective manner.

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