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Metal free biomimetic deaminative direct C–C coupling of unprotected primary amines with active methylene compounds†

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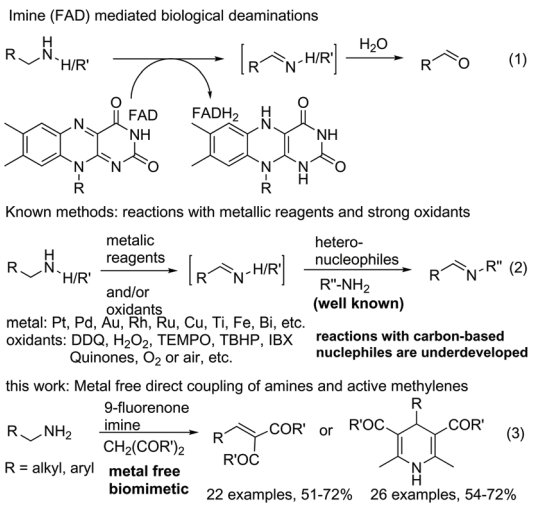
An unprecedented direct C–C coupling reaction of unprotected primary amines with active methylene compounds is reported. The reaction involves a biomimetic deamination of amines which was achieved under conditions free of metallic reagents and strong oxidizing agents. A wide range of primary amines was reacted with different active methylene compounds to provide structurally diverse trisubstituted alkenes and dihydropyridines. A kinetic study revealed an activation barrier of 10.1 kcal mol^{-1} for the conversion of a key intermediate of the reaction.

Monoamine oxidase (MAO) oxidizes a variety of primary and secondary amines, polyamines, and amino acids in the biological system. Flavin adenine dinucleotide (FAD) acts as the coenzyme for these deamination reactions. In the first step, an amine is dehydrogenated to form an imine while FAD is reduced to $FADH_2$. The imine is hydrolyzed subsequently to produce the corresponding carbonyl compounds (Scheme 1, eqn (1)).[1]

A large number of methods have been developed for the transformation of amines to imines (eqn (2)). The reported methods for the conversion of amines to the corresponding imines employed stoichiometric/catalytic amounts of oxidants[2] (*e.g.* IBX, DDQ, iminoquinone, *etc.*) and metallic reagents or catalysts[3] (*e.g.* Ru, Pt, Rh, Au, *etc.*) in the presence or absence of oxidants. Molecular oxygen or air was also used as the oxidant for the amine to imine oxidation in the presence of metallic reagents.[4] Aerobic photooxidation of primary benzylamines using catalytic amounts of hindered acridinium salts, $BiVO_4$ or Ru-based complex was also reported.[5] These methods are efficient, but often require harsh reaction conditions, strong oxidants, metallic reagents, and other additives.

In most of the aforementioned methods, the amine functionality was converted to the corresponding imine, nitrile or aldehyde (eqn (2)).[2–5] In some cases, the imine formed was subsequently reacted with heteronucleophiles to produce the corresponding imidazole, oxazole, thiazole or quinoxaline.[6] However, the reaction of the imine generated *in situ via* dehydrogenation of an amine with the carbon-based nucleophile like an active methylene compound is uncommon.[7] Moreover, to the best of our knowledge, no report on the direct coupling of unprotected primary amines with active methylene compounds producing alkenes and dihydropyridines is known in the literature. This is probably because the active methylene compounds are susceptible towards oxidation/decomposition under strong oxidizing conditions.[8] Moreover, propensity towards the over-oxidation of amines to nitriles and high nucleophilicity of free primary amines put further challenges for the success of C–C coupling of free primary amines and active methylene compounds. Therefore, the development of a method that can operate under mild conditions without the aid of strong oxidants and metallic reagents would allow the



Scheme 1 Dehydrogenation of amines and subsequent coupling reactions.

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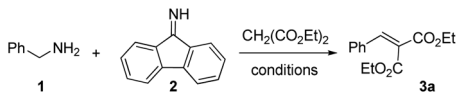
subsequent one-pot reaction of imines with suitable nucleophile like active methylene compounds.

Along the line of our interest for the development of metal- and hazardous oxidant-free organic transformations,[9] we have developed a biomimetic deaminative coupling of primary amines with active methylene compounds using a simple imine derivative as the FAD mimic under conditions free of strong oxidizing agents and metallic reagents (eqn (3)).

Our investigation started with a reaction of benzylamine (**1**), 9-fluorenone imine (**2**) and diethyl malonate in refluxing toluene under an argon atmosphere. The desired alkene **3a** was isolated with 35% yield after 12 h of reaction (Table 1). The yield of the product increased to 68% when the reaction was carried out for a longer time (48 h). However, the same reaction performed at room temperature did not provide the desired product. Different reaction conditions, such as solvents, temperatures, reactant stoichiometry, reaction time, *etc.*, were evaluated to increase the yield of the alkene. Solvents with low boiling points provided lower yields as compared to toluene and xylene. The addition of inorganic/organic bases with either catalytic or stoichiometric amounts did not improve the yield of the product. Interestingly, the use of 9-fluorenone, replacing 9-fluorenone imine, did not yield the desired alkene under the same conditions. However, reaction in the presence of 9-fluorenone-1-carboxylic acid provided the desired product with 25% yield.

The scope of the metal-free deaminative coupling of amines was tested next. Different aryl and heteroaryl amines reacted smoothly to produce the corresponding trisubstituted alkenes **3b–r** with good yields (Table 2). Various functional groups

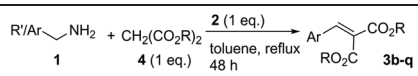
Table 1 Optimization of biomimetic deaminative direct coupling reaction of benzyl amine[a]



Entry	Conditions	Yield[b] (%)
1	Toluene, reflux, 12 h	35
2	Toluene, reflux, 48 h	70
3[c]	Toluene, reflux, 48 h	70
4	Toluene, reflux, 60 h	69
5	Toluene, rt, 12 h	0
6	Xylene, reflux, 48 h	68
7	DCE, reflux, 48 h	40
8	MeOH, reflux, 48 h	20
9	DMF, reflux, 48 h	55
10	Benzene, reflux, 48 h	50
11	DCM, reflux, 48 h	15
12	Toluene, reflux, 48 h, Et_3N (1 eq.)	69
13	Toluene, reflux, 48 h, DBU (1 eq.)	65
14	Toluene, reflux, 48 h, KOH (1 eq.)	30
15	DMF, reflux, 48 h, K_2CO_3 (1 eq.)	64
16	Toluene, reflux, 48 h, NaH (1 eq.)	40
17	THF, reflux, 48 h	50

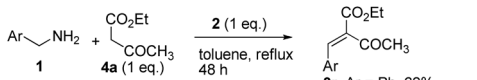
[a] 1 eq. (0.56 mmol) of benzyl amine, 1 eq. of 9-fluorenone imine (0.56 mmol) and 1 eq. of diethyl malonate were (0.56 mmol) reacted. [b] Isolated yield. [c] 1.2 eq. of 9-fluorenone imine was used.

Table 2 Scope for the olefin syntheses



Entry	Ar/R′	R	Alkene	Yield (%)
1	4-Me-Ph	Et	**3b**	67
2	4-MeO-Ph	Et	**3c**	64
3	4-Cl-Ph	Et	**3d**	69
4	4-CF_3O-Ph	Et	**3e**	68
5	4-F-Ph	Et	**3f**	68
6	2-F-Ph	Et	**3g**	60
7	2-Cl-Ph	Et	**3h**	65
8	2-MeO-Ph	Et	**3i**	70
9	3,4-Cl-Ph	Et	**3j**	65
10	3-MeO-Ph	Et	**3k**	64
11	Ph	Me	**3l**	62
12	2-MeO-Ph	Me	**3m**	63
13	Ph	Bn	**3n**	64
14	2-MeO-Ph	Bn	**3o**	72
15	2-Furyl	Et	**3p**	60
16	^{n}Bu	Et	**3q**	51

(*e.g.*, OR, NR_2, F, Cl) in the aromatic ring of arylmethyl amines were tolerated under these reaction conditions. Substrates having both electron-donating (*e.g.*, Me, OMe) and electron-withdrawing (*e.g.*, F, Cl) groups were efficiently reacted to produce the desired products. Heteroarylmethyl amines also participated in the reaction to produce the desired compound **3p** with good yield under the optimized reaction conditions. Alkyl amines also successfully participated in the reaction to provide the desired alkene **3q**. In addition to the symmetrically substituted malonates, unsymmetrical malonates such as ethyl acetoacetate (**4a**) reacted smoothly to produce the desired products **3r** (1.3 : 1) and **3s** (1.5 : 1) as the mixture of *E*/*Z*-isomers (eqn (4)). Interestingly, the reaction with malonic acid (**4b**) afforded cinnamic acid derivatives **3t–u** with good yields (eqn (5)). Additionally, the reaction was found to be effective in gram-scale synthesis, which indicated its potential for practical application (see Scheme s1†).



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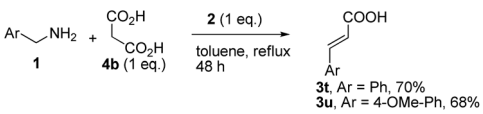
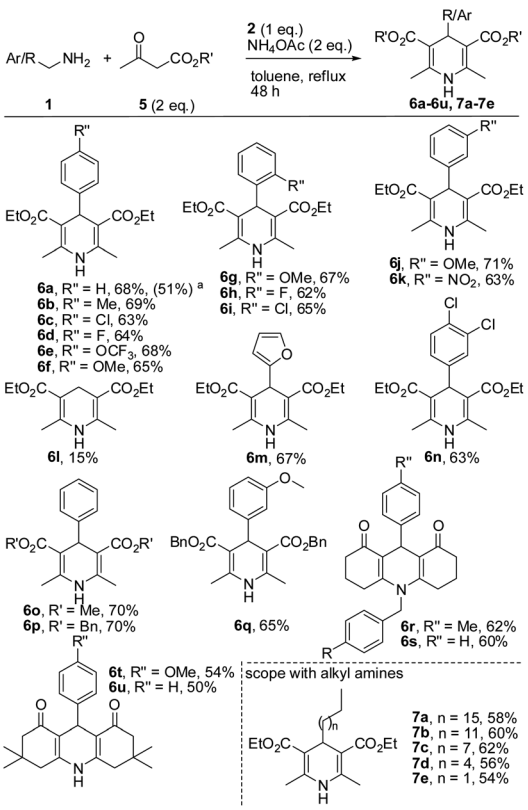


(5)

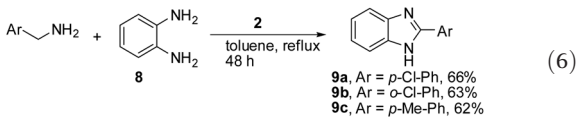
The classical method for the preparation of 1,4-dihydropyridines involves the pseudo four component condensation reaction of an aldehyde, acetoacetic ester, and ammonia or amines.[10] The Knoevenagel condensation product of acetoacetic ester and aldehyde acts as the key intermediate in the reaction. As this novel deaminative coupling reaction produces the related alkene, the scope of this method for the synthesis of 1,4-dihydropyridines was investigated next (Table s1†). The coupling reaction in the presence of 9-fluorenone imine releases one equivalent of ammonia. Therefore, on employing

our deaminative coupling reaction, the dihydropyridines can be synthesized without using an additional ammonia source. As expected, the reaction of benzylamine, ethyl acetoacetate (**5**, R′ = Et), and 9-fluorenone imine (**2**) in the absence of an additional ammonia source provided the desired dihydropyridine **6a** with a maximum yield of 51% (Table s1,† entry 7). Various reaction conditions were screened to increase the yield of dihydropyridines. However, the addition of ammonium acetate as the additional ammonia source increased the yield of the desired product (68%). Large varieties of benzylamines containing both electron-withdrawing and electron-donating groups in the aryl moiety reacted efficiently to provide the desired 1,4-dihydropyridines **6a–6u** with good yields (Scheme 2). Other than ethyl acetoacetate, methyl and benzyl acetoacetate also reacted smoothly to produce the corresponding dihydropyridines **6o–6q**. The reaction with dimedone provided the expected tricyclic dihydropyridines **6t–6u**. Interestingly, simple 1,3-cyclohexadienone gave the *N*-benzylated dihydropyridines **6r–6s** with good yields.

In addition to the benzylamines, alkyl amines with varying chain lengths participated in the reaction to produce the corresponding dihydropyridines **7a–7e** with good yields. Interestingly, a simple methyl amine acted as the substitute of formaldehyde to afford the desired dihydropyridine **6l**, however, with poor yield.



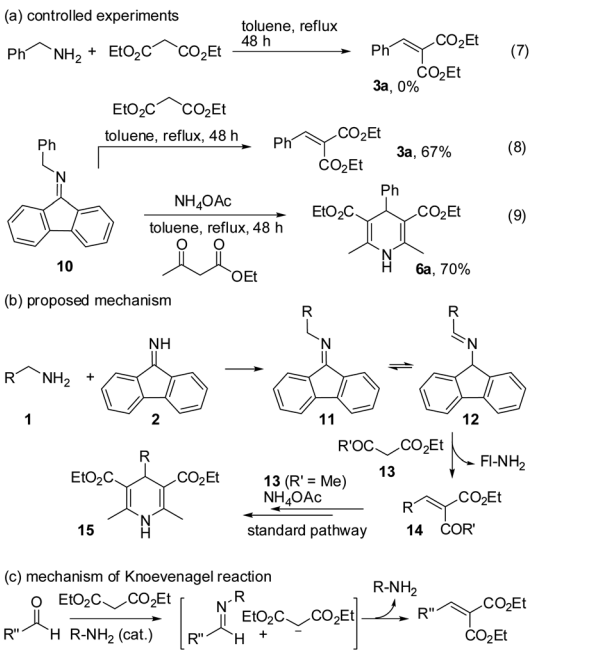
Scheme 2 Scope for the synthesis of dihydropyridines. [a] Reaction was carried out in the absence of NH_4OAc (see Table s1†).



After the success of direct coupling of the amine with a carbon-based nucleophile, the possibility of the reaction with hetero-dinucleophiles was investigated. Accordingly, benzimidazole derivatives **9a–c** were formed, when 2-amino aniline **8** was reacted with an amine and **2** under the same reaction conditions (eqn (6)).

Additional reactions were conducted to understand the possible reaction pathway (Scheme 3a). The reaction in the absence of 9-fluorenone imine (eqn (7)) did not provide the desired coupling product. In addition, a pre-formed imine provided the desired products **3a** and **6a** from separate reactions under standard conditions (eqn (8) and (9)). These results indicate that the 9-fluorenone imine is essential for the reaction and the reaction proceeded *via* imine intermediate **10**.

On the basis of experimental evidence, a plausible mechanism for the metal-free deaminative direct coupling of a primary amine with active methylene compounds is proposed in Scheme 3b. The condensation of amine **1** and 9-flurenone imine (**2**) occurred to provide the corresponding ketimine **11**. The isomerization of **11** furnished the regioisomeric aldimine **12** (identified by NMR, see Fig. s1†) which on subsequent reaction with active methylene compound **13** provided the corresponding alkene **14**. The related addition reaction of the active methylene compound to an imine/iminium ion is well known in primary/secondary amine-catalyzed Knoevenagel reactions.[11] However, in this reaction, the addition of the active



Scheme 3 (a) Controlled experiments. (b) Proposed mechanism of C–C coupling of amines and active methylene compounds. (c) Mechanism of Knoevenagel reactions. Fl-NH_2 = 9-aminofluorene.

methylene compound occurs to the amine carbon in contrast to Knoevenagel reactions where addition occurs to carbonyl carbon (Scheme 3c). In the reaction with acetoacetate, the corresponding alkene reacted further with ammonia, which was either generated during the condensation of **1** and **2** or from NH_4OAc, and another equivalent of acetoacetate to provide the dihydropyridines following the standard pathway.

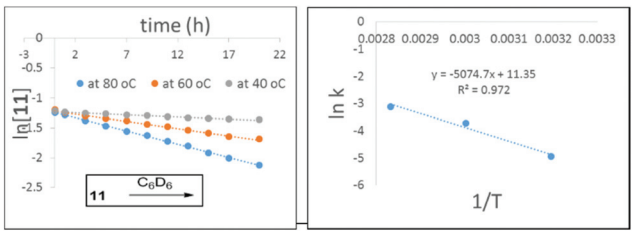
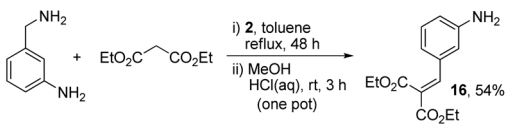


Fig. 1 The rate of the conversion of ketamine **11**. The concentration of **11** was determined using triphenyl methane as the internal standard (see the ESI† for details).

The kinetics of the conversion of key intermediate **11** of the reaction was investigated with the help of ^{1}H-NMR spectroscopy (Fig. 1). It was observed that the rate of the conversion of imine **11** follows a first order kinetics with a rate constant of 4.4×10^{-2} h^{-1} at 80 °C. The rate decreases with the decrease in the reaction temperature. The activation energy for this conversion (10.1 kcal mol^{-1}) was found from the slope of the Arrhenius plot.



(10)

The direct coupling of amino benzylamine with diethyl malonate followed by a mild acid hydrolysis gave alkene **16** having amine functionality with good yield (eqn (10)). The use of a classical reaction of aminoaldehyde, which is not readily available, could be problematic because of its propensity towards polymerization. Therefore, incorporation of the amino group into the dihydropyridine and alkene necessities the reduction of the corresponding nitro compounds using harsh conditions (Zn–AcOH or Sn–HCl).[12] Thus, our method can be applied as an advantageous alternative to the classical condensation of an aldehyde with the active methylene compounds.

In conclusion, we have developed a novel method for direct C–C coupling of primary amines with active methylene compounds to obtain alkenes and dihydropyridines which are traditionally accessed from the reaction of an aldehyde and active methylene compounds. Biomimetic deamination of primary amines under mild conditions, which is free of metallic reagents or catalysts and strong oxidizing agents, allowed the subsequent reaction of resulting imines with the activated methylene compounds. The conversion of ketamine followed a first order kinetics with an activation barrier of 10.1 kcal mol^{-1}. This non-classical approach for the synthesis of alkenes and dihydropyridines starting from primary amines would bring the diversity in synthetic planning.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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