Catalyst-free C–N bond formation under biocompatible reaction conditions†

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A C–N bond formation reaction under biocompatible conditions for the amination of allenic ketone compounds to access a diversity of β-keto enamines is developed. This reaction is atom economical, green, and highly regioselective and works well with many structurally important amines such as amino sugar and amino acid esters or peptides. A wide array of β-keto enamines was obtained in modest to excellent yields with wide functional group tolerance using this protocol. A gram-scale synthesis of an antimicrobial agent was also realized using this strategy under green reaction conditions.

The development of new, clean and biocompatible reactions for green pharmaceutical and biomolecule conjugate synthesis is one of the most challenging endeavors in organic synthesis. Accordingly, there has been much effort directed towards the development of new organic transformations that are highly chemoselective, and work in aqueous media and under mild reaction conditions. Among them, the carbon–nitrogen bond formation reaction has attracted the most attention since the amino group features widely in many pharmaceuticals and bioconjugates such as drugs,1,2 glycoconjugates, antibody conjugates, etc. (Fig. 1). Unfortunately, most of the reported methods for C–N bond forming reactions require the use of expensive metal catalysts, work under harsh reaction conditions, suffer from poor atom economy and are not environmentally friendly. As such, there is an urgent need to develop a metal-free and highly chemoselective C–N bond formation reaction that can work under biocompatible reaction conditions. If successful, this newly developed method will provide efficient and green access to many pharmaceuticals. In addition, bioconjugation with proteins can be potentially achieved where the tertiary structure of proteins can be preserved during the process of the reaction.

Over the years, our group and others have contributed significantly to the green chemistry field through the development of catalyst-free water-based reactions. These include C–C bond forming reactions via the Mukaiyama-aldol strategy,3 and C–P and C–S bond reactions4,5 with allylic alcohols, using activated dichloro-acetophenones6 and 2H-azirines7 as linkers for disulphide bioconjugation. Inspired by our previous work on C–S bond formation reactions5 with allenic amide as an efficient linker for cysteine bioconjugation, we envisage that amines may react with highly reactive allenic carbonyl compounds under biocompatible conditions to yield the corresponding enamines which are also versatile building blocks for pharmaceutical synthesis (Fig. 2).

The amino functional group features in many bioconjugation reactions with biomolecules such as proteins. As such, there has been a considerable amount of attention paid to amino chemical conjugation strategies such as lysine conjugation. The most common lysine conjugation strategies are conjugation with the N-hydroxysuccinimide (NHS) ester,
Fig. 2  C–N bond formation reaction via allenic ketones and amines under biocompatible conditions.

isocyanates, isothiocyanates, 4-azidobenzozy fluoride (ABF) etc. While these strategies offer great selectivity and are carried out under biocompatible conditions, isolation of the desired product can prove to be cumbersome. Therefore, there is an urgent need to achieve a strategy that works under both green and biocompatible conditions while ensuring that the entire process is easy to operate, and is able to isolate the pure products without the need for liquid–liquid extraction or column chromatography.

Table 1  Optimization of the aza-Michael reaction

| Entry | Solvent          | Time (h) | Conversion (%) | Yield (%) |
|-------|------------------|----------|----------------|-----------|
| 1     | PhCF₃            | 12       | 100            | 82        |
| 2     | Et₂O            | 12       | 100            | 70        |
| 3     | EtOAc           | 12       | 100            | 80        |
| 4     | CH₃CN           | 12       | 100            | 75        |
| 5     | EtOH            | 12       | 100            | 67        |
| 6     | H₂O             | 12       | 100            | 35        |
| 7     | PBS buffer (pH 7.0) | 12       | 100            | 51        |
| 8     | PBS buffer (pH 8.0) | 12       | 100            | 55        |
| 9     | PBS buffer (pH 8.0) | 12       | 100            | 58        |
| 10    | PBS buffer (pH 8.0) | 12       | 100            | 59        |
| 11    | PBS buffer (pH 8.0) | 1        | 100            | 79        |
| 12    | PBS buffer (pH 8.0) | 0.67     | 100            | 81 (70)   |

* Experimental conditions: 1a (0.20 mmol) and 2a (0.30 mmol) in the specified solvent (2 mL) at room temperature. * Conversions and yields were determined by °H NMR using CH₃J as the internal standard. 1.0 equiv. of 2a was used. * Conversions and yields were determined by °H NMR using CH₃J as the internal standard. * Isolated yield.
was obtained in 67% yield when a heterocyclic allenic ketone was employed in the reaction. The presence of an alkyne in the substrates (3ac and 3ad) did not appear to hinder the outcome of the reaction; the desired enaminones were obtained in 90% and 45% yields, respectively. Aliphatic allenic ketones (3ae–3ah) also reacted smoothly to afford the corresponding enaminones in modest to excellent yields.

The synthetic utility of the enaminones was subsequently explored (Fig. 3). Enaminone 3a was thiolated with Lawesson’s reagent to afford enaminothione 4 in 59% yield.10 Treating enaminone 3a with the phenyl vinyl ketone gave the corresponding cyclohexa-1,3-diene 5 in 56% yield.11 A gram-scale synthesis of the anti-microbial drug 6 was realized under benign conditions, yielding the desired product in 90% yield by removing the solvent under reduced pressure. Enaminone 3ac can participate in a Cu(I)-catalyzed [3 + 2] cycloaddition12 with tosyl azide to give compound 7 in 88% yield. Enaminone 3ac can also undergo a click reaction5c with the anti-viral drug, Zidovudine,13 giving compound 8 in 27% yield.

The proposed mechanism for the formation of the enaminone is illustrated in Fig. 4. The initial aza-Michael attack by the nucleophilic benzylamine regioselectively at the β-position of the allenic ketone 1a afforded an enol intermediate. This enol tautomer was proposed to be stabilized through a
six-membered transition state via intramolecular hydrogen bonding, which readily tautomerized to yield (Z)-enaminone 3a exclusively as the desired product.

In summary, we have developed a practical and efficient strategy for the amination of allenic ketones in a green and biocompatible manner. The reaction is carried out in a phosphate buffer system (pH 7–8) under catalyst-free conditions and at room temperature. The special features of this method are: (1) no protection of sensitive functional groups is required; (2) applicable for glycoconjugation; (3) dual-linker functionality; (4) gram scale synthesis of an anti-microbial agent with no usage of metals and organic solvents and no column chromatography is required for its purification. With this novel strategy, we have once again taken a step towards increasing our toolbox of green synthetic and bioconjugation methods.

Conflicts of interest
There are no conflicts to declare.

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