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The bioinspired design of a reagent allows the functionalization of C_α–H of α,β-unsaturated carbonyl compounds *via* the Baylis–Hillman chemistry under ambient conditions†

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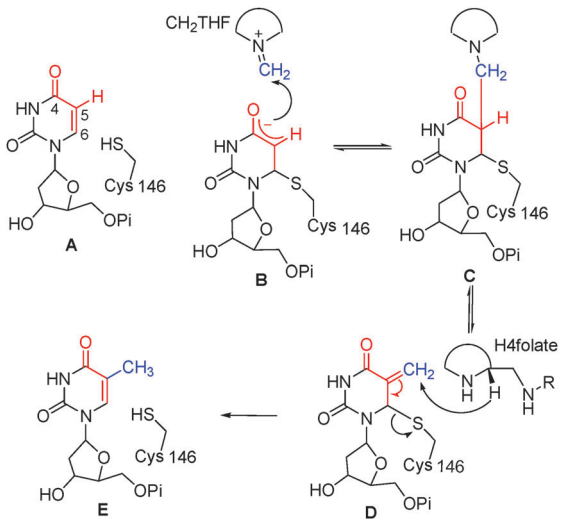
A rationally designed reagent capable of affecting alkylation at C_α of α,β-unsaturated carbonyl compounds is reported. The reaction proceeded at room temperature without any additives. The pH and H-bond formation during the reaction play a key role in the working of the reagent.

Carbon–carbon bond formation is one of the fundamental reactions in organic chemistry for which a variety of strategic approaches have been adopted.[1] In the last few decades, the functionalization of the C–H bond of arenes with C-substituents for preparing useful compounds has drawn great attention.[2] However, the selective activation of a specific C–H bond and the reaction conditions to tolerate the additional functionality within the molecule pose great challenges. In continuity with the synthetic approaches for C–C bond formation, the α,β-unsaturated carbonyl system is another possible substrate that is part of many natural products[3] and useful synthons/compounds could be synthesized if we achieved the C–H functionalization of this class of compounds. Although the C–C bond formation between an α,β-unsaturated carbonyl compound (activated alkene-nucleophile) and an aldehyde (electrophile) is excellently accomplished through the Baylis–Hillman reaction,[4] this synthetic approach does not cover extensively the alkylation/acylation reactions at C_α of the nucleophile.[5] Instead, Funk *et al.* achieved the preparation of 2-alkyl/acylpropenals by thermolysis of 5-substituted-4*H*-1,3-dioxins.[6]

When analyzing the enzymatic reactions, we found that the thymidylate synthase (TSase) catalyzed conversion of 2′-deoxyuridine-5′-monophosphate (dUMP) to 2′-deoxythymidine-5′-monophosphate (dTMP) is an excellent example of C–H functionalization probably involving the Baylis–Hillman chemistry.[7] In this biochemical reaction, the α,β-unsaturated carbonyl system constituted by the O=C_4–C_5=C_6 fragment of the uracil moiety is activated by the Cys residue and the resulting enolate captures a methylene group from CH_2THF – overall the α-H of the α,β-unsaturated carbonyl system is replaced with the CH_3 group (Scheme 1).[7d,f] Inspired by this natural endeavour and the results of our recent experiments,[8] it was envisaged that reagent **1** could conveniently be used for C_α–H functionalization of α,β-unsaturated carbonyl compounds (Fig. 1).



Scheme 1 TSase catalyzed conversion of dUMP to dTMP. The part of uracil moiety which is undergoing chemical change is shown in red.

We initially investigated the reaction between acrolein and reagent **1** (Table 1) (R=CH_3, the ester form was preferred to avoid any interference with $CysS^-$). The progress of the reaction was monitored using high resolution mass spectra besides the use of thin layer chromatography. The formation of a new product (TLC) was observed after 30 min of the reaction at pH 8.0 (25–28 °C) with the new peak in the HRMS of the reaction mixture at *m*/*z* 485.1482 corresponding to the *m*/*z* of adduct **4** (calcd *m*/*z* 485.1489, $[M + H]^+$) (Fig. S4, ESI†). We then added CH_3I to the reaction mixture at pH 8.0. The formation of a new species with *m*/*z* 499.1636 was detected (Fig. S5, ESI†) but

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† Electronic supplementary information (ESI) available: General procedure, mass spectra, NMR spectra. See DOI: 10.1039/c5cc08830e

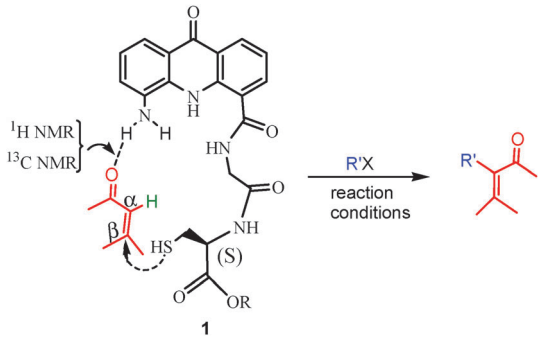
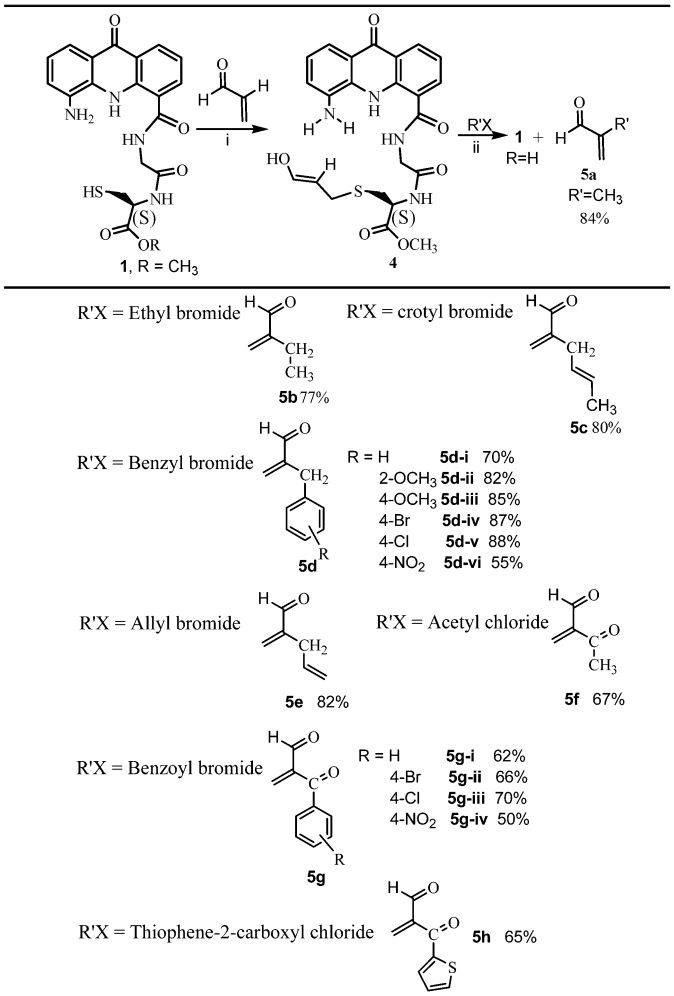


Fig. 1 An overview of the reactions presented in this communication.

Table 1 Investigation of the reaction of acrolein with reagent **1** and further reaction of adduct **4** with various alkylating agents (R′X)



Reaction conditions: (i) DMSO-H_2O (1:4), pH 8.0, 25-28 °C, stir, 30 min
(ii) DMSO-H_2O (1:4), pH 8.0, stir, 40 min, pH 9.5, stir, 1h

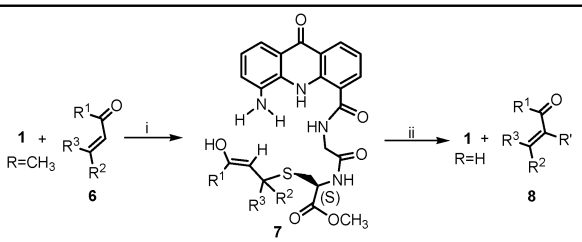
there was no further change in the reaction even after 3 h of stirring. We changed the pH of the reaction to 9.5. After 1 h of stirring the reaction mixture at pH 9.5, product **5a** was released from reagent **1** (Table 1) (Fig. S6, ESI†). This result is particularly significant because it is the first example of the TSase inspired Baylis–Hillman reaction that proceeds under ambient conditions without using any metal catalyst.

In order to explore the versatility of adduct **4** to react with other electrophiles, it was treated with ethyl bromide, crotyl bromide, benzyl bromide, allyl bromide, acetyl chloride, benzoyl chloride and thiophene-2-carboxyl chloride. After stirring the reaction mixture for 1 h at pH 9.5, the corresponding products **5**(**b**–**h**) were produced in moderate to high yields (Table 1, Fig. S7–S21, ESI†). An electron-donating or -withdrawing substituent on the benzene ring of benzyl- and benzoyl-chloride was tolerated in this reaction. It was noticed that the steric hindrance gained when shifting from an alkylating group to an arylating group did not affect the yield of the arylated product.

Next, we investigated the scope of this reaction with other α,β-unsaturated carbonyl compounds under the optimized reaction conditions (Table 2, Fig. S22–S33, ESI†). Crotonaldehyde, cinnamaldehyde, mesityl oxide and 4-phenylbut-3-en-2-one coupled smoothly with reagent **1**. The methylation and allylation also proceeded with no trouble and the corresponding product **8** with anti-configuration at C=C (nOE data, ESI†) was isolated. Probably, the discrimination between the two faces of the substrate due to the H-bonding between the carbonyl *O* of the substrate and the NH_2 of the reagent was responsible for the formation of single geometrical isomer of products **8**.

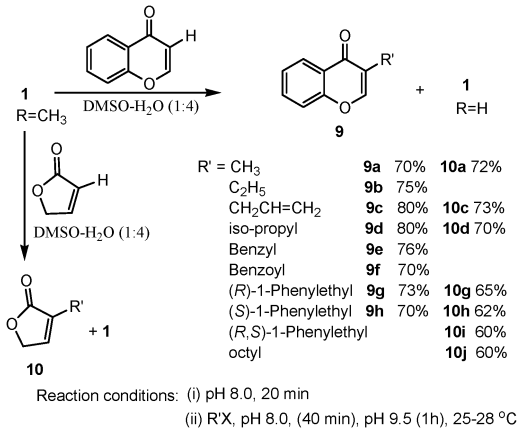
Enthused by the results of the forgoing experiments, the cyclic substrate such as chromone was also investigated for

Table 2 Reaction of reagent **1** with α,β-unsaturated carbonyl compounds and further reaction of adduct **7** with alkylating agents



6	7	
(a) crotonaldehyde	R^1 = H, R^2 = H, R^3 = CH_3	**8a** i, R' = CH_3 (73%); ii, R' = CH_2-CH=CH_2 (78%)
(b) cinnamaldehyde	R^1 = H, R^2 = H, R^3 = Ph	**8b** i, R' = CH_3 (68%); ii, R' = CH_2-CH=CH_2 (70%)
(c) mesityl oxide	R^1 = CH_3, R^2 = CH_3, R^3 = CH_3	**8c** i, R' = CH_3 (65%); ii, R' = CH_2-CH=CH_2 (66%)
(d) 4-phenylbut-3-en-2-one	R^1 = CH_3, R^2 = H, R^3 = Ph	**8d** i, R' = CH_3 (70%); ii, R' = CH_2-CH=CH_2 (70%)

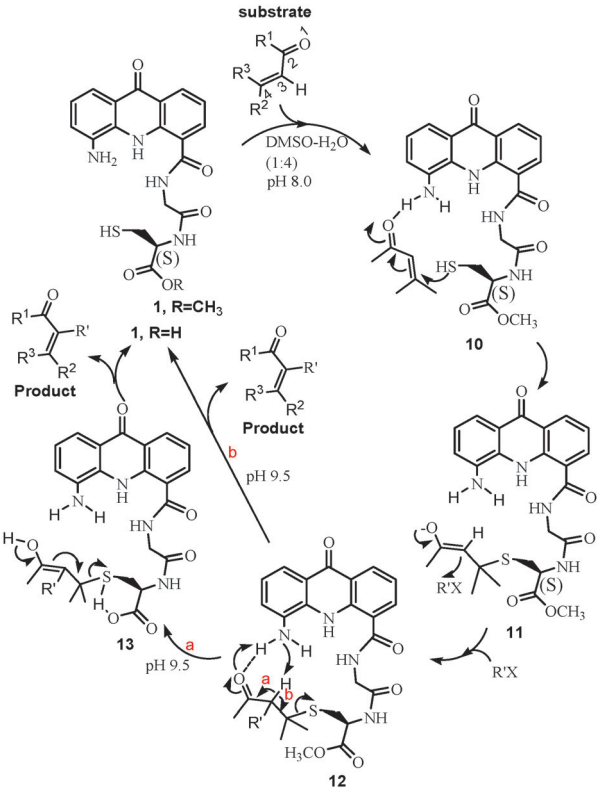
Reaction conditions:
(i) DMSO-H_2O(1:4) pH 8.0,20 min
(ii) R'X, pH 8.0 (40 min), pH 9.5 (1h), 25-28 °C



Scheme 2 Alkylation of chromone and 2(5*H*)-furanone.

reaction with reagent **1** (Scheme 2, Fig. S34–S41, ESI†) followed by the treatment with alkylating agents. We procured product **9** from this reaction. With enantiomerically pure (*R*)-1-bromoethyl benzene and (*S*)-1-bromoethyl benzene, the products (−)(*S*)-**9g** and (+)(*R*)-**9h** were obtained. The assignment of the *R*/*S* configuration is tentative assuming the mechanism to be S_N2. Further extending the synthetic application of the reagent **1**, lactone in the form of 2(5*H*)-furanone was also alkylated at the C3 carbon and compound **10**, including one carrying octyl group (**10j**), were obtained (Scheme 2, Fig. S42–S47, ESI†). As evidenced by the HRMS and NMR spectra, no ring opening was observed in the case of chromone and 2(5*H*)-furanone based products **9** and **10**.

Mechanistically, the H-bond formation between the carbonyl group of the substrate and the NH_2 group on acridine seems to trigger the reaction of $CysS^-$ of **1** (R═CH_3) at C4 of the substrate. This was evidenced by (i) the observation that the reaction progresses at pH 8.0, (ii) the downfield shifting of the NH_2 signal of the acridone in ^{1}H NMR spectrum of the reaction mixture containing reagent **1** and acrolein (the substrate) (Fig. S48, ESI†), (iii) the downfield shift of C2 of acrolein in the ^{13}C NMR spectrum of the reaction mixture (Fig. S48, ESI†) and (iv) no reaction of compound **2** (Fig. S49, ESI†) with any one of the α,β-unsaturated carbonyl compounds studied here. The reaction of enolate **11** with the alkylating agent (most probably through the S_N2 mechanism, ESI†) takes place at pH 8.0. The H-bond seems to play a crucial role in the removal of C2–H as the reaction in DMSO–D_2O proceeds at a considerably low rate and takes 6 h for the formation of the product (Fig. S50, ESI†) (kinetic study will be given separately). Since no further change was observed in the reaction mixture after the formation of species **12**, the conversion of the ester group of **1** (R═CH_3) to the carboxyl group at pH 9.5 might have provided H-bond assistance to the *S*-bridge and either through route 'a' (intermediacy of **13**) or through route 'b'; we found that within 1 h, compound **1** (R═H) was formed along with the formation of the product **5**/**8**/**9**/**10** (Scheme 3). The role of stereochemistry at C_α of the Cys residue of reagent **1** (R═CH_3) was justified when the desired coupling reaction, however, did not occur at all in the presence of compound **3** (Fig. S49, ESI†).



Scheme 3 Plausible mechanism for **1** (R═CH_3) mediated C_α alkylation of α,β-unsaturated carbonyl compounds.

In summary, we demonstrated that the Nature inspired reagent **1** (R═CH_3) provided the first example of metal free C_α-alkylation/acylation of α,β-unsaturated carbonyl compounds. The reaction tolerated a wide range of substitutions on the core fragment and proceeded at room temperature in good yields. These findings suggest the usefulness of natural synthetic protocols for laboratory synthesis. Further synthetic applications of this approach and kinetic studies are ongoing in our laboratory.

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