Organic LETTERS

Letter

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A Chemoselective Route to β-Enamino Esters and Thioesters

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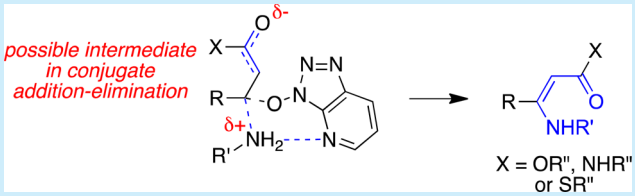
Supporting Information

ABSTRACT: Conditions were developed for syntheses of β-enamino esters, thioesters, and amides. These reactions involve hydroxybenzotriazole derivatives in buffered media. Illustrative syntheses of some heterocyclic systems are given, including some related to protein−protein interface mimics.



β-Enamino esters **A** are versatile synthons for many heterocycles and benzenoid compounds. There are too many applications of these building blocks to cite them all, but illustrative ones include syntheses of amino-furanones, indoles,[1] oxazoles,[2] pyrazoles,[3] pyridines[4] and dihydropyridines,[5] pyrimidineones,[6] pyrroles,[7] and quinolines[8] (Figure 1). Existing

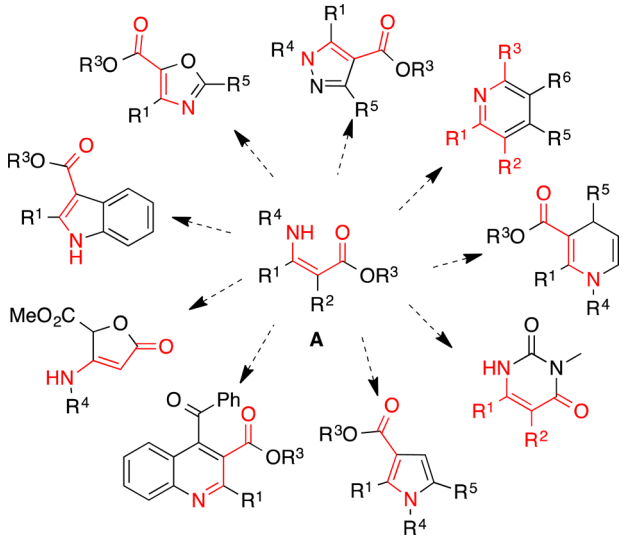
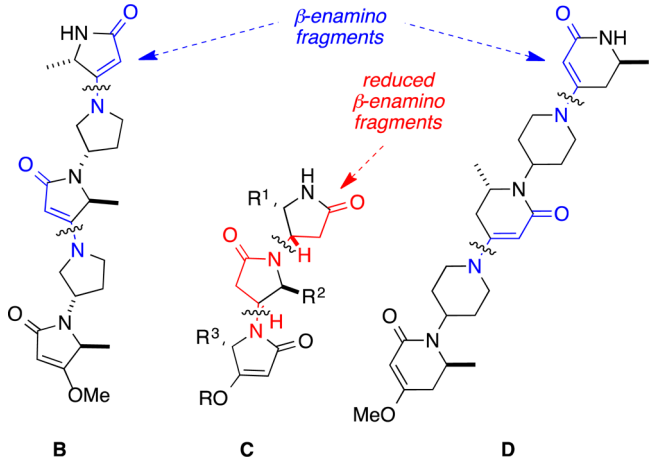


Figure 1. Illustrative uses of β-enamino esters.

methods to prepare β-enamino carbonyl derivatives were summarized in two papers.[9] These methods tend to involve acids, elevated temperatures, and oxidizing agents, *i.e.* characteristics that limit the range of products that can be formed.

Our interest in β-enamino derivatives arose when pursuing the interface mimics **B**,[10] **C**,[11] and **D**.[12] Scaffolds **B**−**D** have several β-enamino amide functionalities, and overall yields in their syntheses are directly related to efficient formation of the bonds indicated. Consequently, we accumulated experience with methods for efficient formation of β-enamino derivatives under mild conditions. This *Letter* summarizes the most important of those findings.



Apparently the literature on formation of β-enamino esters from β-keto esters contains few, if any, references to conditions most commonly associated with amide bond couplings. We envisaged these types of conditions might be effective, and data from exploratory experiments to test this hypothesis are shown in Table 1 (a full description is in the Supporting Information). These pilot reactions were performed on phenolic esters to allow the opportunity for the amines to displace phenoxide, *ie* a more stringent chemoselectivity test than if less reactive esters were used. In the event, such acylation reactions did not account for significant product formation under the best conditions identified.

Together, entries 1−5 of Table 1 indicate HOAt (1-hydroxy-7-azabenzotriazole)[14] is preferred as an additive over HOBt or DMAP. Entry 7, compared with all the others, strongly indicates that a weak base is required. Chloroform seems to be a better solvent for this reaction type than dichloromethane or DMF (*cf.* entries 8 and 12 vs 5 and 9). The best yield was obtained using EDC·HCl (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride) in entry 8, but the PyBOP ((benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluoro-

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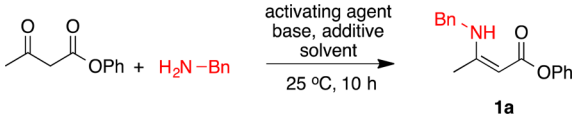
Table 1. Pilot Reactions for Formation of β-Enamino Derivatives



1a

entry	activating reagent	base	solvent	additive	yield (%)
1	EDC·HCl	TEA	CH_2Cl_2	HOBt	11
2	EDC·HCl	$KHCO_3$	CH_2Cl_2	–	12
3	EDC·HCl	$KHCO_3$	CH_2Cl_2	DMAP	17
4	EDC·HCl	$KHCO_3$	CH_2Cl_2	HOBt	74
5	EDC·HCl	$KHCO_3$	CH_2Cl_2	HOAt	85
6	EDC·HCl	imidazole	CH_2Cl_2	HOAt	71
7	EDC·HCl	–	CH_2Cl_2	HOAt	33
8	**EDC·HCl**	**$KHCO_3$**	**$CHCl_3$**	**HOAt**	**93**
9	EDC·HCl	$KHCO_3$	DMF	HOAt	13
10	HBTU[13]	$KHCO_3$	$CHCl_3$	–	60
11	PyBOP	$KHCO_3$	$CHCl_3$	–	80
12	**PyBOP**	**imidazole**	**$CHCl_3$**	–	**87**

phosphate)[15] conditions in entry 12 were only marginally inferior and sometimes, depending on the substrate, have advantages with respect to workup simplicity. Figure 2 shows products and yields for other β-enamino esters formed via the method illustrated in entry 12.

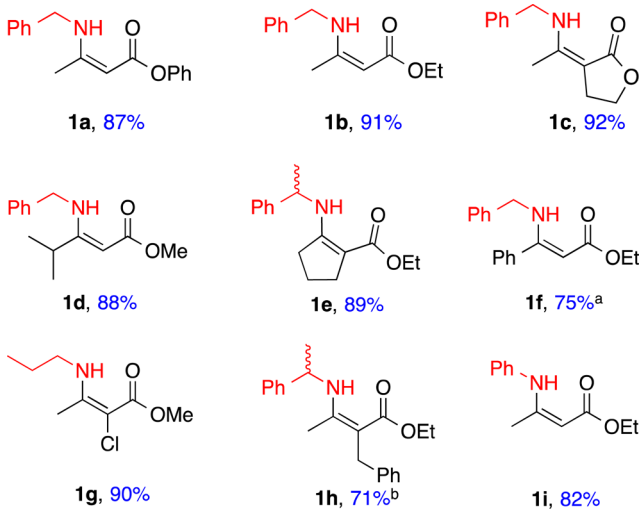
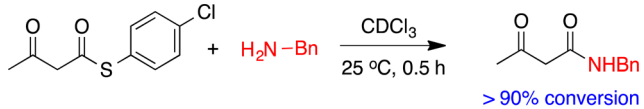


Figure 2. β-Enamino esters formed using the conditions shown for entry 12 in Table 1, with the following exceptions: [a] 36 h; [b] 2 equiv of amine and 24 h.

The next step in this study was to investigate β-ketothioesters as substrates. Reaction 1 illustrates how, in the absence of an



reaction 1

additive, an amine is preferentially acylated by a β-ketothioester, rather than condensing with it. It is potentially valuable to be able to invert this chemoselectivity because that would enable preparation of β-enamino *thioesters*. Previous syntheses of β-enamino thioesters are limited to the *N*-unsubstituted forms (via multistep procedures,[16] or by adding ammonia under buffered conditions[17]) or via condensations of *tert*-butyl β-ketothioesters in the presence of ceric ammonium nitrate (CAN) where the large *S*-alkyl group attenuates the reactivity of the thioester.[9b]

Inverted chemoselectivity relative to the reaction above was achieved by modifying the Table 1, entry 12 conditions to include the acid HOAt and hydrogen carbonate buffer. This enabled syntheses of the β-enamino thioesters shown in Figure 3.

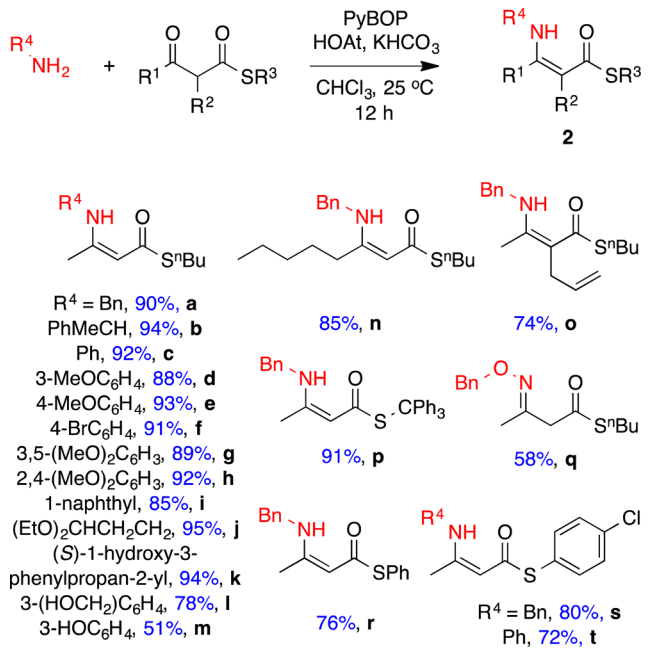


Figure 3. Illustrative uses of β-enamino *thioesters*.

Figure 3 demonstrates that both aliphatic and aromatic amines can be used as the nucleophile in these reactions. Formation of the β-enamino thioesters **2j** and **2p** indicates that acetal and *S*-trityl groups are tolerated, whereas they presumably would not be in the presence of acids. Products **2k**, **2l**, and **2m** demonstrate primary alcohols and phenols are compatible with the featured condensation reaction. Phenylthio ester products **2r–t** were formed, even though PhS^- is a better leaving group than in the other reactions.

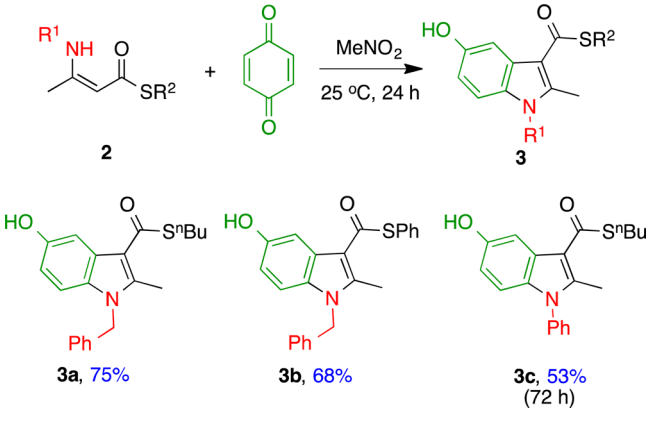


Figure 4. Illustrative Nenitzescu indole syntheses.

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Three Nenitzescu indole syntheses[18] were performed to illustrate how β-enamino thioesters can be used (Figure 4).[19] All three reactions did not perturb the thioester functionality, even when this involved a more reactive phenylthiolate leaving group, *i.e.* for indole **3b**. Formation of the regioisomers shown was confirmed via NOESY experiments.

An isolable intermediate azabenzotriazole ether was formed when 1,3-cyclohexanedione was allowed to react under the conditions used under typical coupling conditions (Figure 5). It

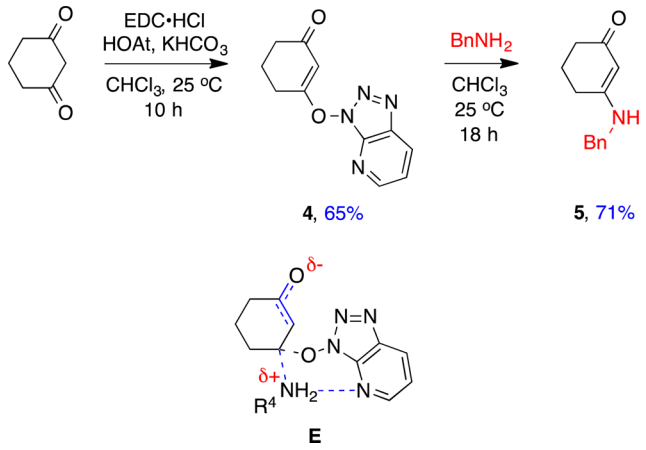

Figure 5. Intermediate formation in HOAt-mediated reactions.

seems probable that this intermediate is more stable than the corresponding one in the thioester reactions. If similar intermediates are formed throughout, this reaction indicates a two-step conjugate addition−elimination process is operative. This would also explain why HOAt is superior to HOBt in these transformations: because the aza-derivative can "lever" proton transfer in the amine addition step as indicated in transition state **E**.

Finally, Figure 6 illustrates how the conditions developed for formation of β-enamino amides were applied in reactions typical of those used to make the interface mimics **B**−**D**. Good yields were obtained, and the near-neutral conditions indicate there is likely to be a broad substrate scope.

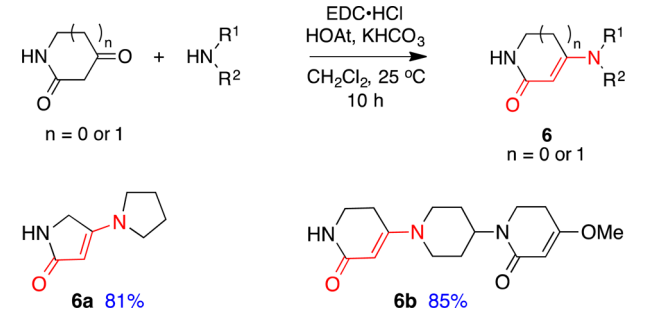

Figure 6. Application of the featured conditions for syntheses of interface mimic fragments.

In summary, β-enamino derivatives can be formed via carefully buffered conditions featuring activation agents such as EDC·HCl and PyBOP. These conditions are sufficiently mild to facilitate synthesis of a wide range of examples, including relatively delicate synthons like β-enamino thioesters.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

In honor of Alan R. Katritzky, 18 Aug. 1928−10 Feb. 2014.

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