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A Method for the Preparation of β-Amino-α,β-unsaturated Carbonyl Compounds: Study of Solvent Effect and Mechanism

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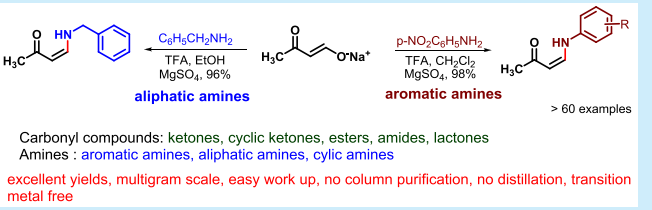
ABSTRACT: An efficient method for the preparation of β-amino-α,β-unsaturated carbonyl compounds is demonstrated. Bench-stable sodium 3-oxo-enolates were prepared from carbonyl compounds, and reacted with amines in the presence of an acid and a desiccant. DFT studies revealed contrasting mechanisms toward the reactivity of aliphatic amines in protic solvents and aromatic amines in aprotic solvents. While the former proceeds through the formation of an imine, the latter passes through the Michael addition−elimination mechanism.

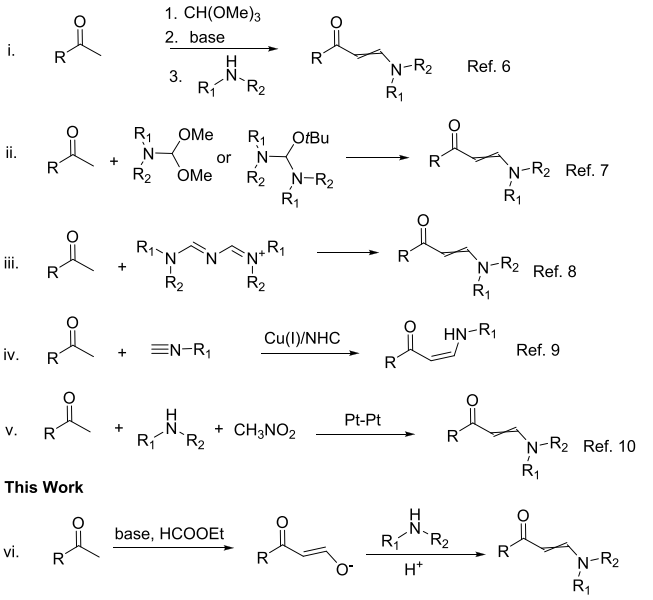


β-Amino-α,β-unsaturated carbonyl compounds (enaminones) are powerful synthons in organic chemistry. The presence of multifunctional groups and heteroatoms in enaminones facilitate multiple nucleophilic and electrophilic additions at different positions to produce complex molecular structures.[1] Enaminones are well utilized in the preparation of electron-rich dienes for Diels−Alder reaction[2] and in synthesis of various heterocyclic and carbocyclic compounds.[3] β-Amino-α,β-unsaturated carbonyl functionality is an integral part of several bioactive natural products.[4]

Purification of enaminones is a tedious job since they are mostly unstable on silica gel for chromatographic purification or require extreme care for fractional distillation. Hence, it is highly desirable to develop methods that can produce enaminones obviating the need of purification. Herein, an improved method with systematic investigation is presented for the preparation of enaminones. Bench-stable and easily accessible sodium 3-oxo-enolate derivatives of carbonyl compounds were used as reactive intermediates, with various amines in the presence of an acid and a desiccant. The products obtained after hydrocarbon extraction were found to be pure.

Scheme 1 shows various methods, which directly use carbonyl compounds as substrates for the synthesis of enaminones.[2c,5−11] Each of these methods has its own drawback, either limiting to carbonyl part or limiting to amine part. For instance, cyclic ketones can be accessed with only few methods,[12] whereas few methods are applicable only for arylketones.[9,10,13] Moreover, other functional enaminones obtained from esters, amides, lactones, and lactams can be accessed only by few methods with great limitations. Many such methods also show limitations toward amine functionality; for example, methods ii, iii, and v lead to enaminones derived only from secondary amines, while method iv provides enaminones of primary amine derivatives. To the best of our knowledge, no single report describes the synthesis of enaminones from all class of carbonyl compounds using a wide range of amines. Despite, the well-known application of sodium-3-oxo enolates as reactive

Scheme 1. Direct Conversion of Carbonyl Compounds to Enaminones by One-Carbon Homologation Amination



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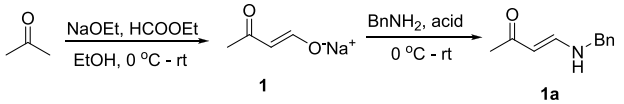
intermediates in preparation of enaminones,[5,7] no systematic investigations have been carried out to apply this method to wide range of substrates and no proper mechanistic studies are reported.[7]

The present study started by examining a model reaction between sodium (*E*)-3-oxobut-1-en-1-olate[14] **1** with benzylamine in the presence of a Brønsted acid to produce enaminone **1a** (entries 1−11, Scheme 2). Among many acids,

Scheme 2. Preparation of (*E*)-4-(Benzylamino)but-3-en-2-one from Acetone*



1 1a

entry	acid	solvent	drying agent	yield(%)[a]
1.	PTSA	EtOH	-	92%[c]
2.	CSA	EtOH	-	50%
3.	TFA	EtOH	-	96%[c]
4.	H_2SO_4	EtOH	-	40%
5.	HCl	EtOH	-	60%
6.	CF_3SO_3H	EtOH	-	70%
7.	HCOOH	EtOH	-	62%
8.	CH_3COOH	EtOH	-	72%
9.	Citric Acid	EtOH	-	75%
10.	H_3PO_4	EtOH	-	80%
11.	Oxalic acid	EtOH	-	61%
12.	TFA (1.5eq)	EtOH	Na_2SO_4	96%[c]
13.	TFA (0.6 eq)	EtOH	Na_2SO_4	56%
14.	TFA	DCM	Na_2SO_4	81%
15.	TFA	$CHCl_3$	Na_2SO_4	76%
16.	TFA	MeOH	Na_2SO_4	88%
17.	TFA	*t*-BuOH	Na_2SO_4	85%
18.	TFA	*i*-PrOH	Na_2SO_4	87%
19.	TFA	EtOH	$MgSO_4$[b]	98%[c]
20.	TFA	EtOAc	$MgSO_4$	80%
21.	TFA	acetone	$MgSO_4$	65%
22.	TFA	CH_3CN	$MgSO_4$	48%
23.	TFA	EtOH	$CaSO_4$	70%
24.	TFA	EtOH	4Å MS	80%

*Reaction conditions: amine (2 mmol), salt (2.5 mmol), solvent (10 mL/mmol), and acid (3 mmol), 0 °C to rt, 14 h. [a]Yields after Kugelrohr distillation; [b]Method A: reaction conducted with 1 equiv of amine, 1.2 equiv of sodium salt **1**, 1.5 equiv of acid, and $MgSO_4$ (1 g/mmol) in anhydrous ethanol. [c]No change in yields before and after Kugelrohr distillation.

TFA and PTSA provided better results for enaminone **1a** with 100% conversion of amine. It was also observed that the results for the same reaction were inconsistent from batch to batch. The liberated water molecule during condensation, preventing the reaction either by quenching the acid or by diverting the reaction for unwanted byproducts.[15] After screening several dehydrating agents $MgSO_4$ was found as an effective desiccant (entry 19, Scheme 2) to remove water and to drive the reaction in a clean manner.[16] Under the standard reaction conditions using method A, the product **1a** was produced on multigram scale (10 g, 98% yield) after hydrocarbon extraction. The purity of the product was estimated by NMR analysis using an internal standard. Further, compound **1a** was directly treated with Boc anhydride to obtain *N*-boc protected enaminone $\mathbf{1a}_{Boc}$ in 96% yield after chromatographic purification, confirming the formation of **1a** in pure form.[17]

Similarly, other primary amines upon reaction with enolate **1** produced enaminones **1b**−**1m** in 84−98% isolated yields. Use of amino acid derivatives such as amino esters, amino alcohols and amino amide provided chiral enaminones (**1k**−**1n**) in very good to excellent yields. Likewise, the reaction of salt **1** with secondary amines and cyclic amines provided products **1o**−**1u**, mainly as *E*-enaminones. After the successful conductance of the reaction with different amines and enolate **1**, further we prepared the enolates **2**, **3**, **4**, and **5** from acetophenone, 3-pentanone, 4-phenyl-2-butanone, and aceto-2-nathone, respectively. Enolate **2**, showed very good reactivity toward all classes of amines to produce enaminones **2a**−**2e** in very good to excellent isolated (84−96%) yields. Compounds **3**, **4**, and **5** with benzylamine provided **3a**, **4a**, and **5a** (85%, 88%, and 92% yields). Similarly, enolates **6** and **7** prepared from cyclopentanone and cyclohexanone upon reaction with various amines following method A produced enaminones **6a**−**6e** and **7a** and **7b** in very good to excellent yields.[18]

In the process of systematic investigation, we prepared lithium and potassium salts from acetophenone.[19] When compared with sodium salt, lithium salt is more stable, and less moisture sensitive whereas potassium salt is hygroscopic. The reaction of lithium and potassium salts with benzylamine produced product **2a** in 46% and 66% respectively with large amount of unidentified byproducts. It was clear that counterion Na^+ is more appropriate to provide adequate stability for enolate and to facilitate the reaction under optimized conditions. Apart from success with two step procedure, a one-pot method[20] was also tried by the in situ preparation of sodium salt **1** followed by sequential addition of desiccant, amine, and acid, but it provided lesser conversion and moderate yields of enaminone **1a** (70%).[21]

Surprisingly, reaction of aniline with compound **1** in ethanol did not provide the desired enaminone **1aa** (Figure 1). The reversal of reactivity of aniline from general trend may be attributed to the decreased nucleophilicity of anilines. This was evident from the enhanced reactivity of aniline with sodium salt **1** in aprotic solvent (dichloromethane) under same reaction conditions, which produced enaminone **1aa** as an exclusive product (method B, Scheme 3). Our results indicate that the excellent reactivity of aliphatic amines in protic solvent (ethanol) is due to the stabilizing hydrogen bonding influence of the solvent on reaction intermediates and transition states whereas for aromatic amines a preference of aprotic solvent suggests a totally different mechanistic pathway for the formation of enaminones.

Following method B, other anilines with electron-donating groups yielded *Z*-selective enaminones[18] **1ab**−**1ae** in 96−98% yields. The more challenging electron-deficient anilines such as 2-bromoaniline, 4-cyanoaniline, and 4-nitroaniline[6b,22,23] provided enaminones **1af**, **1ag**, and **1ah**[23] in excellent yields (97%, 87%, 98%) under mild reaction conditions. Similarly, *N*-methylanilines upon reaction with enone **1** provided enaminones **1ai** and **1aj** in excellent yields with *E*-selectivity. The sodium salts of acetophenone, cyclopentanone and cyclohexanone derivatives also exerted same reactivity with aniline to provide enaminones **2aa**, **2ab**, **6aa**, and **7aa**.

After successful results with ketones, other carbonyl compounds such as esters, lactones, and amides (Figure 2) were converted to their corresponding enaminones using

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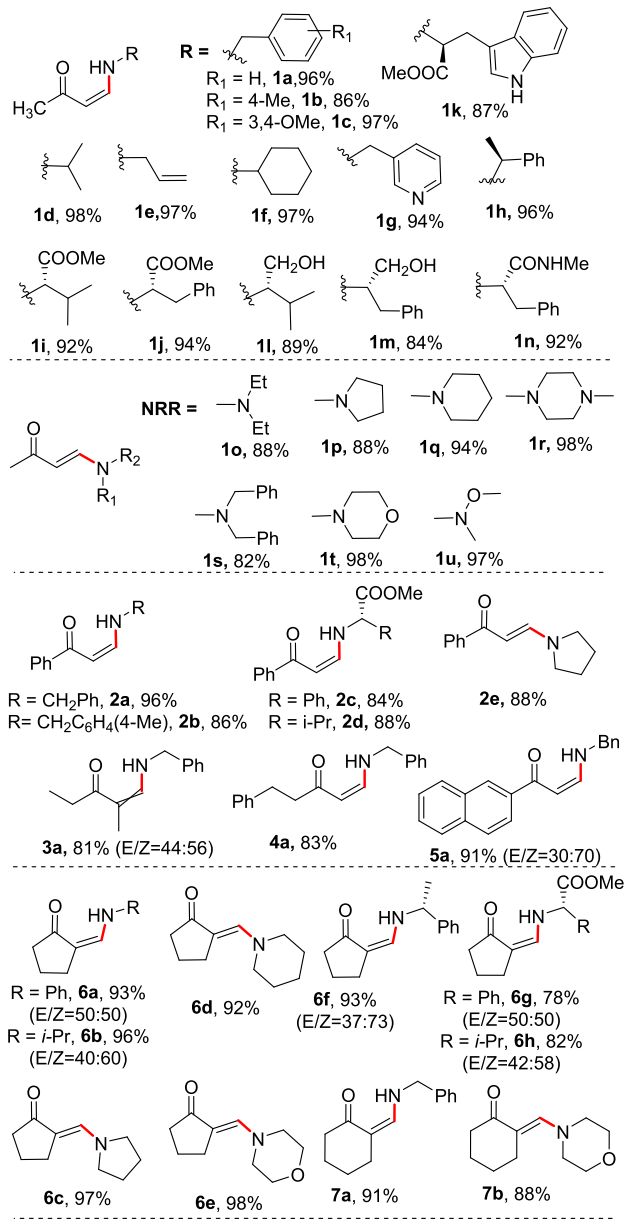
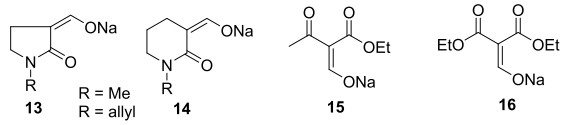
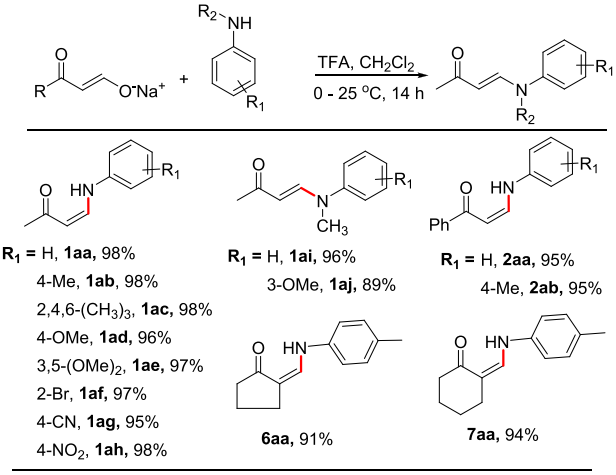


Figure 1. Enaminones prepared from enolates of ketones with various amines.

method A for aliphatic amines and method B for aromatic amines. Enamino esters (**8a**, **8b**, and **8aa**) from ethyl acetate,[24] enamino lactones (**9a**, **10a**, and **10aa**) from butyrolactone and velarolactone, and enamino amides (**11a**, **12a**, **12b**, and **12aa**) from *N*,*N*-dimethylacetamide and *N*-phenyl-*N*-methylacetamide were isolated in excellent yields (Figure 2). Enolates prepared from lactams such as compounds **13** and **14** upon reaction with amines did not provide any enamino derivatives even after prolonged reaction times and heating conditions. Similarly, the sodium salts **15** and **16** obtained from 1,3-dicarbonyl compounds did not provide any desired enaminone.



Scheme 3. Reaction of Enolates of Various Ketones with Aromatic Amines[a]



[a]Method B: reaction conducted with 1 equiv of aniline, 1.2 equiv of sodium salt **1**, 1.5 equiv of acid, and $MgSO_4$ (1 g/mmol) in dichloromethane (10 mL/mmol).

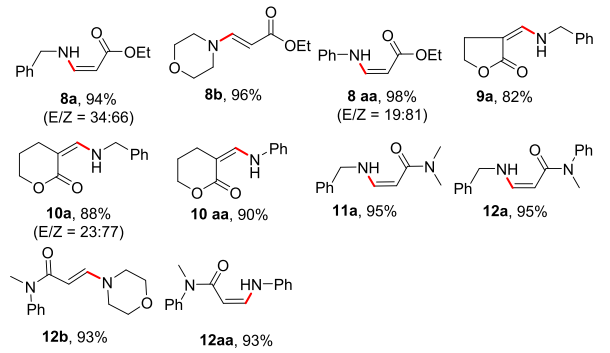


Figure 2. Enaminones prepared from enolates of esters, lactones, and amides with various amines.

Addition of TFA to sodium (*E*)-3-oxobut-1-en-1-olate (**1**) gives 4-hydroxybut-3-en-2-one (**I**). B3LYP/SMD/6-311+G-(d,p) level DFT calculation[25] shows that enol form of **I** ($\mathbf{I}_{enol}$) has the "*Z*" configuration due to intramolecular OH···O hydrogen bond (Figure 3) while aldehyde form ($\mathbf{I}_{ald}$) is 2.6 kcal/mol higher in energy in ethanol. The NMR experiments also proved the *Z*-configuration of $\mathbf{I}_{enol}$ by observing two olefinic signals at δ 5.63 and 7.97 as doublets with J = 4.5 Hz whereas the signals at δ 3.59 and 9.78 indicated the presence of tautomer $\mathbf{I}_{ald}$; the enol to aldehyde ratio being 10:1 at room temperature. For the reactions conducted in ethanol with primary amines, formation of enaminones through the imine formation is computed using DFT (Scheme 4a). The enol···benzylamine complex (**II**) formation is exothermic by 5.3 kcal/mol owing to the intramolecular OH···N hydrogen bond. The proton transfer from enol to amine is barierless and gives **III** at relative energy (E_{rel}) −6.5 kcal/mol. The quarternized nitrogen in **III** transfers the proton to olefinic carbon via **ts2** with activation energy (E_{act}) 11.8 kcal/mol to yield the tautomeric $\mathbf{I}_{ald}$...benzylamine complex **IV** which undergoes nucleophilic addition via **ts3** (E_{act} 3.9 kcal/mol) to yield the zwitterionic product **V** and subsequently a proton transfer in **V** via **ts4** produces the carbinolamine **VI**. Proton transfer appears as a rate-determining step with E_{act} 19.7

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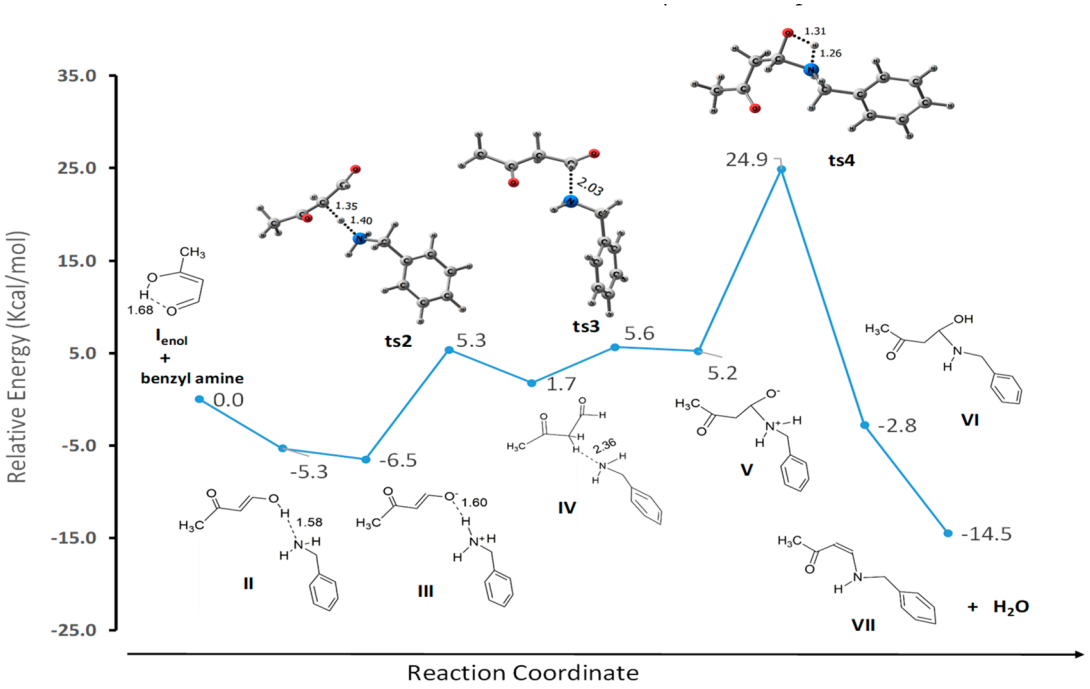

Figure 3. Energy profile for β-enamino carbonyl compound. Transition states in ball and stick model and distances in angstroms.

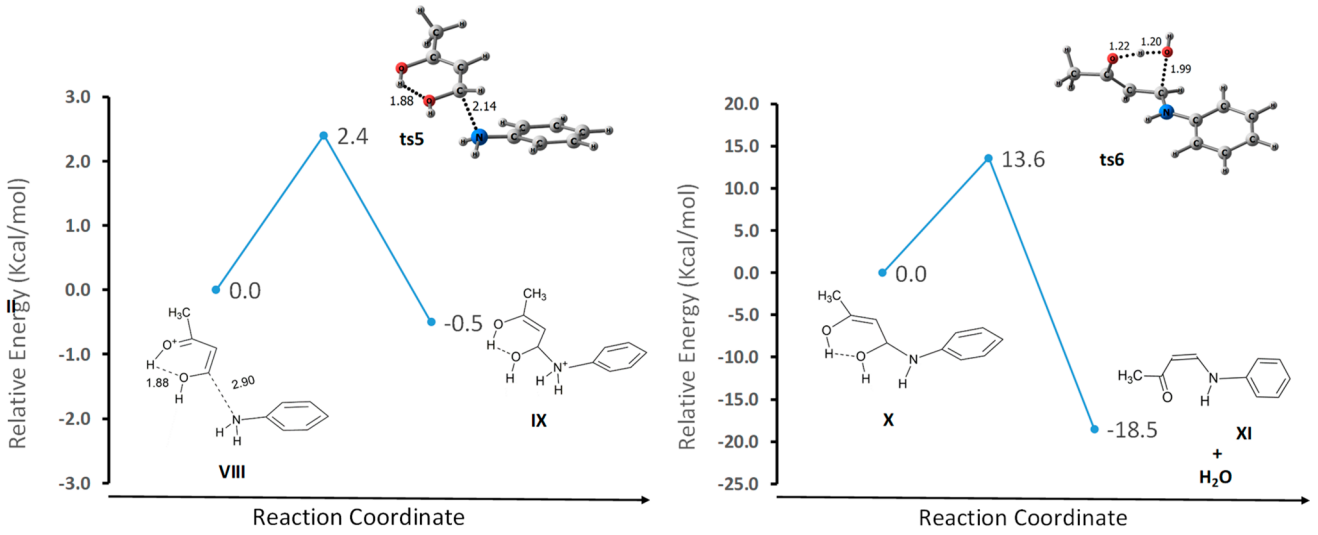

Figure 4. Energy profile for (a) nucleophilic addition of aniline and (b) elimination of water. Transition states in ball and stick model and distances in angstroms.

kcal/mol. The trifluoroacetic acid may assist this proton transfer. Elimination of H_2O in **VI** occurs instantenously by the protonation of its hydroxy group to provide iminium intermediate $\mathbf{VII}_{\text{iminium}}$ to yield the final product, β-enamino carbonyl compound **VII**. The *cis* arrangement of keto and amino group in **VII** is preferred due to the formation of intramolecular H-bond by *Z*-configuration. Overall, the reaction is exothermic by 14.5 kcal/mol. The energy profile clearly suggests that the key step of C−N bond formation via **ts3** is a very facile process and the active form of reactant is $\mathbf{I}_{ald}$. It is worth mentioning that C−N bond formation transition state **ts3** is not observed with the aromatic amine.

In the second possible pathway (Scheme 4b), protonated form of enol, $\mathbf{I}_{enol}{\cdot}H^+$ is the active species which reacts with aniline in dichloromethane. DFT calculations show that $\mathbf{I}_{enol}{\cdot}H^+$ is characterized by an intramolecular O···H hydrogen bond. The prereaction complex $\mathbf{I}_{enol}{\cdot}H^+{\cdots}$aniline (**VIII**) (Figure 4a) undergoes nucleophilic addition of aniline on the CC double bond of $\mathbf{I}_{enol}{\cdot}H^+$ via **ts5** with E_{act} 2.4 kcal/mol to form **IX**. Deprotonation of **IX** gives the hemiaminal compound **X** (Figure 4b). From **X**, elimination of water occurs via **ts6** with E_{act} 13.6 kcal/mol to yield the final product, β-enamino carbonyl compound **XI**. Here too, C−N bond formation is very easy while the rate-determining step is elimination of water. It is notewothy that a transition state similar to **ts5** for nucleophilic addition is not observed with an aliphatic amine. The DFT study clearly suggests that in protic solvent $\mathbf{I}_{ald}$ reacts with aliphatic amine whereas in

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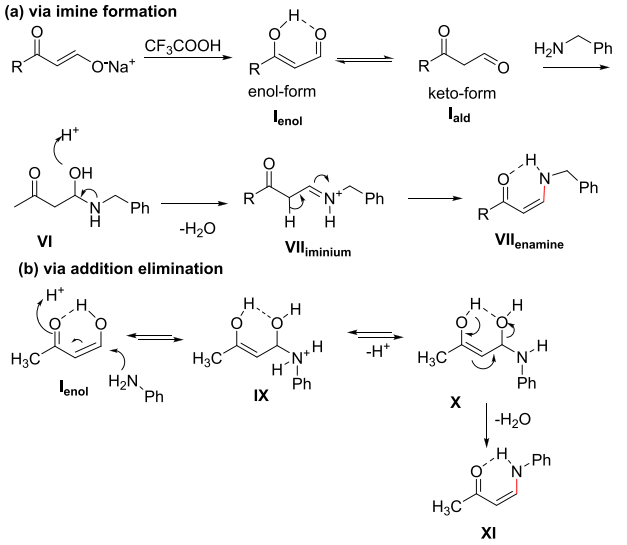
Scheme 4. Possible Mechanism for the Reaction of Enolate 1 with Aliphatic and Aromatic Amines



aprotic solvent $\mathbf{I}_{enol}{\cdot}H^+$ reacts with aromatic amine to yield the final products.

In summary, we have demonstrated a simple and efficient method for the conversion of carbonyl compounds to β-amino-α,β-unsaturated carbonyl compounds using bench-stable sodium enolates under mild reaction conditions. The method is very effective when a desiccant is used to trap the in situ generated water molecule. The method worked well with carbonyl compounds such as ketones, cyclic ketones, esters, lactones and amides along with aliphatic amines, cyclic amines, and anilines. Even very weak nucleophilic amines like 4-nitroaniline and 4-cyanoaniline provided excellent yields. The influence of electronic effects of amines in different solvent systems has been studied, and it has been found that the reaction of aliphatic amines proceeds through the imine formation while aromatic amines pass through the Michael addition−elimination mechanism as supported by DFT mechanistic studies. Clean conversion, easy hydrocarbon extraction, no extra purification, and multigram-scale preparation are shown as practical advantages of the method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04531.

Experimental procedures, spectral data of prepared compounds, and X-ray data of compounds **1ab** and **1ah** (PDF)

Accession Codes

CCDC 1972196 and 1972363 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(11) For other recent reports on synthesis of enaminones: (a) Lee, D.; Kim, S. M.; Hirao, H.; Hong, S. H. *Org. Lett.* **2017**, *19*, 4734−4737. (b) Quinones, R. E.; Glinkerman, C. M.; Zhu, K.; Boger, D. L. *Org. Lett.* **2017**, *19*, 3568−3571. (c) Yu, D.; Sum, Y. N.; Cheng Ean, A. C.; Chin, M. P.; Zhang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 5125−5128. (d) Ueno, S.; Shimizu, R.; Kuwano, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 4543−4545. (e) Xu, X.; Du, P.; Cheng, D.; Wang, H.; Li, X. *Chem. Commun.* **2012**, *48*, 1811−1813.

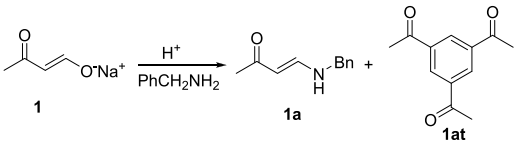
(12) (a) Seki, H.; Georg, G. I. *J. Am. Chem. Soc.* **2010**, *132*, 15512−15513. (b) Miura, T.; Funakoshi, Y.; Morimoto, M.; Biyajima, T.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17440−17443. (c) Reddy, D. S.; Judd, W. R.; Aube, J. *Org. Lett.* **2003**, *5*, 3899−3902. (d) Bejan, E.; Fontenas, C.; Hassan, A. H.; Daran, J. C.; Balavoine, G. G. A. *Eur. J. Org. Chem.* **1999**, 2485−2490.

(13) Li, M.; Fang, D.; Dai, X. *Tetrahedron Lett.* **2017**, *58*, 4747−4749.

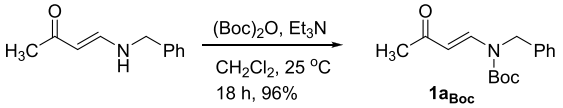
(14) Sodium salt **1** was prepared on 80 g scale; the compound is stable at room temperature, can be weighed in open air, and can be stored for a year in a sealed bottle.

(15) This is similar to the formation of imine where the liberated water molecule needs to be removed azeotropically. Moffett, B.; Hoehn, W. M. *J. Am. Chem. Soc.* **1947**, *69*, 1792−1794.

(16) (a) Yadav, J. S.; Goreti, R.; Pabbaraja, S.; Sridhar, B. *Org. Lett.* **2013**, *15*, 3782−3785. (b) We also observed that $MgSO_4$ effectively prevents the self-trimerization of *β*-ketoaldehyde formed after the addition of acid to produce **1at** (5−20%).

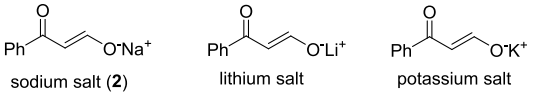


(17)



(18) A general trend is observed for formation of *Z*-selective enaminones with all primary amines. In case of enaminones obtained from 3-pentanone (**3a**), cyclopentanone (**6a, 6b, 6f, 6g, 6h**) and cyclohexanone (**7b**) significant amount of *E*/*Z* ratio is observed.

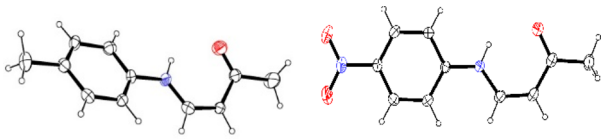
(19) Sodium, lithium and potassium enolate derivatives of acetophenone.



(20) See the Supporting Information for one pot method.

(21) When the reaction was carried out with a large excess of salt (2.5 equiv) and acid (2.8 equiv) with 1 equiv of benzylamine in ethanol, only compound **1a** was observed as the exclusive product without formation of any azabisenone product. It was also observed that the amount of acid alters the rate of the reaction significantly.

(22) The structures of compounds **1ab** and **1ah** were confirmed by X-ray crystallographic analysis.



(23) Chisholm, D. R.; Valentine, R.; Pohl, E.; Whiting, A. *J. Org. Chem.* **2016**, *81*, 7557−7565.

(24) In the case of esters and lactones, the stereochemistry of the products is not very selective and primary amine derivatives **8a**, **8aa**, **9a**, **10a**, and **10aa** are isolated in a significant *E*/*Z* ratio, whereas the secondary amines provided mainly *E*-selective products.

(25) For more details on DFT calculations, see the Supporting Information.

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