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Acetoacetanilides as Masked Isocyanates: Facile and Efficient Synthesis of Unsymmetrically Substituted Ureas

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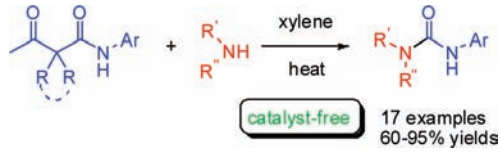
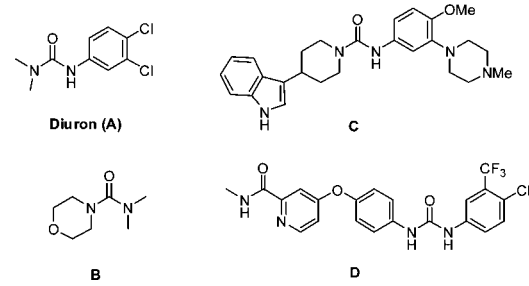
ABSTRACT



A general and practical method for the preparation of unsymmetrically substituted ureas has been developed. By the reactions of acetoacetanilides with various amines including primary/secondary amines, a series of substituted aryl ureas were achieved in high yields. Acetoacetanilide substrates can be considered as masked reagents that liberate reactive isocyanates in situ.

Substituted ureas have received considerable attention due to their wide range of applications in agriculture, petrochemicals, medicine, and biology and as important intermediates and bifunctional organocatalysts in organic synthesis.[1−3] For example, Diuron (**A**) (Scheme 1) is a commercially available herbicide mainly used to control weeds on hard surfaces.[4] Structurally simple urea **B**, incorporating a morpholine ring, was found to be very effective in the treatment of chronic myelogenous leukemia.[5] Unsymmetrically substituted urea **C** has been shown to be a potent HIV-1 protease inhibitor[6] and **D** as a receptor tyrosine kinase (RTK) inhibitor.[7]

Scheme 1. Structures of Biologically Important Substituted Ureas



The conventional methods reported for the urea synthesis are essentially based on phosgene,[8] phosgene substitutes,[9]

(1) For reviews on substituted ureas, see: (a) Gallou, I. *Org. Prep. Proced. Int.* **2007**, *4*, 355. (b) Bigi, F.; Maggi, R.; Sartori, G. *Green Chem.* **2000**, *2*, 140. (c) Vishnyakova, T. P.; Golubeva, I. A.; Glebova, E. V. *Russ. Chem. Rev. (Engl. Ed.)* **1985**, *54*, 249. (d) Matsuda, K. *Med. Res. Rev.* **1994**, *14*, 271.

(2) Selected examples on substituted ureas as intermediates in organic synthesis, see: (a) Gao, J.; Li, H.; Zhang, Y.; Zhang, Y. *Green Chem.* **2007**, *9*, 572. (b) Clayden, J.; Hennecke, U. *Org. Lett.* **2008**, *10*, 3567. (c) Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488. (d) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (e) Yu, S.; Haight, A.; Kotecki, B.; Wang, L.; Lukin, K.; Hill, D. R. *J. Org. Chem.* **2009**, *74*, 9539.

(3) Selected examples on urea-based bifunctional organocatalysts in organic synthesis, see: (a) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (b) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (c) Lubkoll, J.; Wennemers, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6841. (d) Wei, Q.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 1008.

(4) Cabrera, A.; Cox, L.; Velarde, P.; Koskinen, W. C.; Cornejo, J. *J. Agric. Food Chem.* **2007**, *55*, 4828.

(5) Cao, P.; Huang, X.; Ding, H.; Ge, H.; Li, H.; Ruan, B.; Zhu, H. *Chem. Biodiversity* **2007**, *4*, 881.

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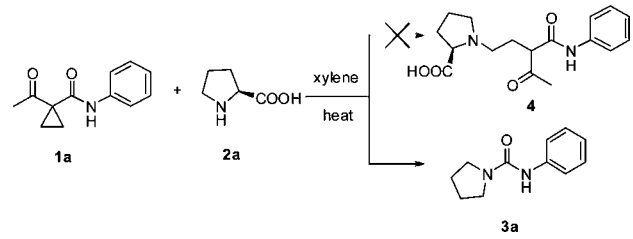
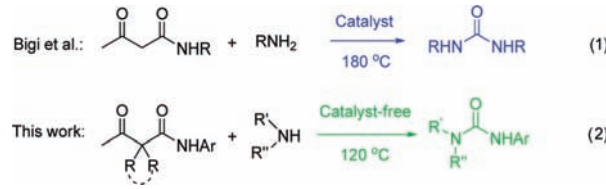
or isocyanates.[10] These approaches have been demonstrated to be particularly efficient for symmetrical ureas. However, phosgene and isocyanates are toxic, unstable, and expensive to handle. In this regard, direct utilization of in situ formed isocyanates represents an attractive strategy toward efficient synthesis of ureas, especially more challenging unsymmetrically substituted ureas.[1a,11]

In our research on the synthetic potential of α,α-disubstituted β-ketoamides[12] bearing both electrophilic and nucleophilic centers toward various carbo- and heterocycles,[13] we presented the amine-mediated ring-opening reactions of doubly EWG-activated cyclopropanes and subsequent recyclization, which afford fully functionalized pyridin-2(1*H*)-ones.[13a] In our continued work, the reaction of 1-acetyl-1-carbamoyl cyclopropane (**1a**) with L-proline was explored (Scheme 2). To our surprise, the expected ring-opening product **4** was not observed. Instead, an unsymmetric *N*-aryl urea[14,15] was achieved in high efficiency, which provides a straightforward, simple, and efficient synthesis of unsymmetrically substituted ureas via in situ formation of isocyanates.[16] A careful literature search revealed that reactions of acetoacetanilides and primary amines have been reported

Scheme 2. Initial Investigation

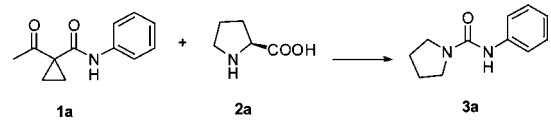


by Bigi et al.[17] It was noteworthy that, in their reactions, the reaction conditions require high temperatures (180 °C) and a zeolite catalyst, and only symmetric *N*,*N*′-dialkyl[17a] (aryl[17b]) ureas were prepared (eq 1). By contrast, a *catalyst-free* reaction of acetoacetanilides and primary/secondary amines was developed under milder conditions in our work (eq 2). Herein, we wish to communicate the results.



Initially, optimization of the reaction conditions was conducted (Table 1). It was found that both the solvent and

Table 1. Optimization of the Reaction Conditions[a]



entry	**2a** (equiv)	solvent	*t* (°C)	time (h)	yield (%)[b]
1	2.2	CH_2Cl_2	rt	8	0
2	2.2	THF	60	8	0
3	2.2	xylene	120	3.5	92
4	1.2	xylene	120	3.5	92
5	1.2	toluene	115	3.5	90
6	1.2	DMF	120	7	trace
7	1.2	H_2O	100	8	0

[a] Reactions were carried out on a 1.0 mmol scale in 2 mL of solvent. [b] Yield of isolated product.

temperature have a large effect on the reaction. Whether at room temperature in CH_2Cl_2 or at 60 °C in THF for 8 h, the reactions of acetoacetanilide **1a** and L-proline **2a** (2.2 equiv) could not give satisfactory results (entries 1 and 2). To our delight, at 120 °C in xylene (2.0 mL) for 3.5 h, the reaction of acetoac-

(6) Matzen, L.; van Amsterdam, C.; Rautenberg, W.; Greiner, H. E.; Harting, J.; Seyfried, C. A.; Böttcher, H. *J. Med. Chem.* **2000**, *43*, 1149.
(7) Wilhelm, S. M.; Carter, C.; Tang, L.; Wilkie, D.; McNabola, A.; Rong, H.; Chen, C.; Zhang, X.; Vincent, P.; McHugh, M.; Cao, Y.; Shujath, J.; Gawlak, S.; Eveleigh, D.; Rowley, B.; Liu, L.; Adnane, L.; Lynch, M.; Auclair, D.; Taylor, I.; Gedrich, R.; Voznesensky, A.; Riedl, B.; Post, L. E.; Bollag, G.; Trail1, P. A. *Cancer Res.* **2004**, *64*, 7099.
(8) (a) Babad, H.; Zeiler, A. G. *Chem. Rev.* **1973**, *73*, 75. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed; Wiley: New York, 2001; p 1191; (c) Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2497.
(9) Majer, P.; Randad, R. S. *J. Org. Chem.* **1994**, *59*, 1937.
(10) The reaction of isocyanates with various nucleophiles has been extensively reported in the literature, see: (a) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457. (b) Braunstein, P.; Nobel, D. *Chem. Rev.* **1989**, *89*, 1927. For the utilization of isocyanate towards the synthesis of eight-membered cyclic ureas via [6 + 2] cycloaddition, reaction with 2-vinylazetidines has been reported. See: (c) Koya, S.; Yamanoi, K.; Yamasaki, R.; Azumaya, I.; Masu, H.; Saito, S. *Org. Lett.* **2009**, *11*, 5438. For the reaction of isocyanatobenzene with lithiated chiral diamine towards chiral ureas, see: (d) Köhn, U.; Günther, W.; Görls, H.; Andersa, E. *Tetrahedron: Asymmetry* **2004**, *15*, 1419.
(11) For recent examples for the preparation of ureas via in situ formation of isocyanate, see: (a) Lebel, H.; Leogane, O. *Org. Lett.* **2006**, *8*, 57170. (b) Dubé, P.; Noah, F.; Nathel, F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622. (c) Peterson, S. L.; Stucka, S. M.; Dinsmore, C. J. *Org. Lett.* **2010**, *12*, 1340.
(12) For selected representative reactions from β-ketoamides, see: (a) Jiang, B.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. *J. Am. Chem. Soc.* **2009**, *131*, 11660. (b) Liéby-Muller, F.; Constantieux, T.; Rodriguez, J. *J. Am. Chem. Soc.* **2005**, *127*, 17176. (c) Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2007**, *129*, 5828. (d) Xiang, D.; Wang, K.; Liang, Y.; Zhou, G.; Dong, D. *Org. Lett.* **2008**, *10*, 345. (e) Lu, B.; Ma, D. *Org. Lett.* **2006**, *8*, 6115. (f) Ramanjulu, J. M.; DeMartino, M. P.; Lan, Y.; Marquis, R. *Org. Lett.* **2010**, *12*, 2270.
(13) (a) Liang, F.; Cheng, X.; Liu, J.; Liu, Q. *Chem. Commun.* **2009**, 3636. (b) Cheng, X.; Liang, F.; Shi, F.; Zhang, L.; Liu, Q. *Org. Lett.* **2009**, *11*, 93. (c) Li, Y.; Liang, F.; Bi, X.; Liu, Q. *J. Org. Chem.* **2006**, *71*, 8006. (d) Zhao, L.; Liang, F.; Bi, X.; Sun, S.; Liu, Q. *J. Org. Chem.* **2006**, *71*, 1094.
(14) For *N*-aryl urea preparation: Lukin, K. A.; Hsu, M. C.; Fernando, D. P.; Kotecki, B. J.; Leanna, M. R. U.S. Pat. Appl.US2007244178.
(15) More recently, *ortho*-directed C−H bond activation and cross-coupling of aryl ureas have emerged. For representative examples, see: (a) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 781. (b) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 4978. (c) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Gair Ford, J.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830.
(16) Examples for the formation of isocyanates from amides under Pd catalysis, see: (a) Furata, T.; Kitamura, Y.; Hashimoto, A.; Fujii, S.; Tanaka, K.; Kan, T. *Org. Lett.* **2007**, *9*, 183. (b) Donati, L.; Michel, S.; Tillequin, F.; Poreé, F.-H. *Org. Lett.* **2010**, *11*, 156.

etanilide **1a** (1.0 mmol) and L-proline **2a** (2.2 equiv) proceeded cleanly to give a white solid after workup and purification. The product was characterized as *N*-phenylpyrrolidine-1-carboxamide **3a** (92% yield, entry 3) on the basis of its spectral and analytical data (see the Supporting Information). The structure of **3a** was further confirmed by the X-ray single-crystal diffraction (Figure 1).[18] The feed amount of L-proline was

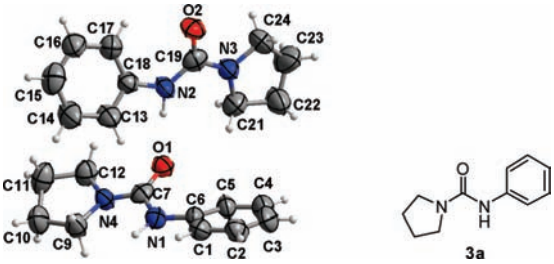


Figure 1. ORTEP drawing of **3a**.

reduced to be 1.2 equiv with a similar yield (entry 4). The reaction in toluene gave a comparable yield (entry 5). Only a trace amount of **3a** was observed when highly polar DMF was used as the solvent under otherwise identical conditions (entry 6). Water was also tested but proved to be inert (entry 7). Obviously, nonpolar solvents like toluene and xylene are favorable for substituted urea formation.

Having established the optimal conditions for the formation of unsymmetrically substituted urea **3a**, a series of reactions based on various substituted acetamides and L-proline were carried out at 120 °C in xylene, with the aim to explore the influence of the substituents on the acetamide substrates on the reactions (Figure 2).[19] As a result, the

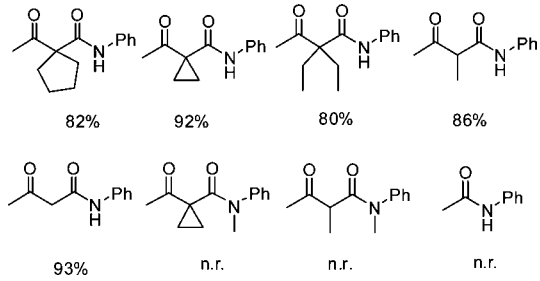
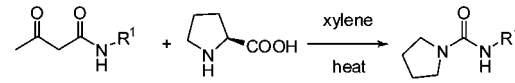


Figure 2. Effect of substituents on the acetamide substrates.

reactions of acetoacetanilides containing various substituents at the α-position, such as cyclopentyl, ethyl, methyl, or hydrogen, proceeded efficiently, giving urea **3a** in good to excellent yields (80−93%). However, *N*-methyl-*N*-phenyl counterparts and *N*-phenylacetamide failed to react with L-proline under identical conditions with intact substrates recovered, which is consistent with the possible mechansim described later.

Since parent 3-oxo-*N*-phenylbutanamide gave satisfactory results, we thus start directly from commercially available substrates to investigate the scope with respect to the amide motif and amine (Tables 2 and 3). First of all, a series of 3-oxo-

Table 2. Reactions of Different Acetoacetanilides and L-Proline[a]



1 2a 3b-k

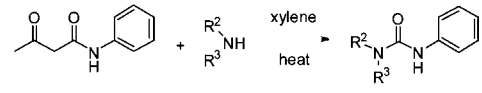
entry	1	R^1	time (h)	3	yield (%)[b]
1	**1b**	2-OmePh	3.0	**3b**	86
2	**1c**	4-OmePh	3.5	**3c**	80
3	**1d**	2-MePh	3.0	**3d**	83
4	**1e**	4-MePh	3.5	**3e**	82
5	**1f**	2,4-Me_2Ph	3.0	**3f**	85
6	**1g**	2-ClPh	3.5	**3g**	80
7	**1h**	4-ClPh	3.5	**3h**	78
8	**1i**	5-Cl-2-OmePh	3.5	**3i**	81
9	**1j**	2-pyridyl	3.5	**3j**	91
10	**1k**	Bn	7	**3k**	0

[a] Reactions were carried out on a 1.0 mmol scale in 2 mL of xylene at 120 °C with **1** (1.0 equiv) and **2** (1.2 equiv). [b] Yield of isolated product.

N-arylbutanamides **1b**−**i** were reacted with L-proline **2a** under conditions identical to those for **3a** in Table 1 (entry 4). It was observed that all the reactions proceeded smoothly to afford the corresponding unsymmetrically substituted aryl ureas **3b**−**i** in good to excellent yields (Table 2, entries 1−8). Heteroaryl urea **3j** was prepared in 91% yield from 3-oxo-*N*-(pyridin-2-yl)butanamide **1j**[19b] (entry 9). When 3-oxo-*N*-alkylbutanamide substrate such as 3-oxo-*N*-benzylbutanamide **1k** was used, the reaction did not give the desired product (entry 10).[20]

Then, various amines including sencondary amines and primary amines were subjected to the reaction sequences (Table

Table 3. Reactions of 3-Oxo-*N*-phenylbutanamide and Various Amines[a]



1a 2 3l-r

entry	2	time (h)	3	yield (%)[b]
1	piperidine	3.0	**3l**	95
2	2-methylpiperidine	3.0	**3m**	92
3	morpholine	3.0	**3n**	95
4	pyrrolidine	3.5	**3a**	87
5	diethylamine	4.0	**3o**	60
6	benzylamine	4.0	**3p**	72
7	aniline	4.0	**3q**	78
8	ammonia	5.0	**3r**	0[c]

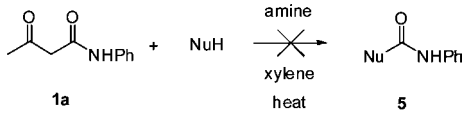
[a] Reactions were carried out on a 1.0 mmol scale in 2 mL of xylene at 120 °C with **1** (1.0 equiv), and **2** (1.2 equiv). [b] Yield of isolated product. [c] NH_4OAc (10.0 equiv) was used as the ammonia source, and the reaction was performed under sealed conditions.

(17) (a) Bigi, F.; Frullanti, B.; Maggi, R.; Sartori, G.; Zambonin, E. *J. Org. Chem.* **1999**, *64*, 1004. (b) Bigi, F.; Maggi, R.; Sartori, G.; Zambonin, E. *Chem. Commun.* **1998**, 513.

3). For secondary cyclic amines such as piperidine, 2-methylpiperidine, morpholine, and pyrrolidine, the reactions were highly efficient, and the desired ureas **3l**−**n** and **3a** were obtained in excellent yields (entries 1−4). Acyclic secondary amines like diethylamine gave the corresponding urea **3o** in moderate yield (entry 5). Primary amines are also efficient for the explored reactions. In the cases of primary aliphatic amines such as benzylamine, and primary aromatic amine such as aniline, the corresponding ureas **3p** and **3q** were prepared in 72% and 78% yields, respectively (entries 6 and 7).[21] However, the reaction of **1a** and ammonia could not give the desired urea **3r** (entry 8). It should be noted that all the crude products **3** could be purified simply by recrystallization from *n*-hexane, which provides a convenience for large-scale synthesis of useful ureas. Gram-scale preparation of compounds **3a** and **3l** have been achieved in respective yields of 86% and 91% in our laboratory. Clearly, the present protocol provides a general, efficient, and practical pathway to construct unsymmetrically substituted aryl ureas. Moreover, the protocol meets the need for library synthesis.

In addition to *N*-nucleophiles, the reactions of *O*/*S*-nucleophiles like BnOH, PhOH, BnSH, and PhSH with acetoacetanilides were also examined, but proved to be inert, even though additional amine like triethylamine (1.2 equiv) or pyrrolidine (0.2 equiv) was introduced to the reaction system (Scheme 3).

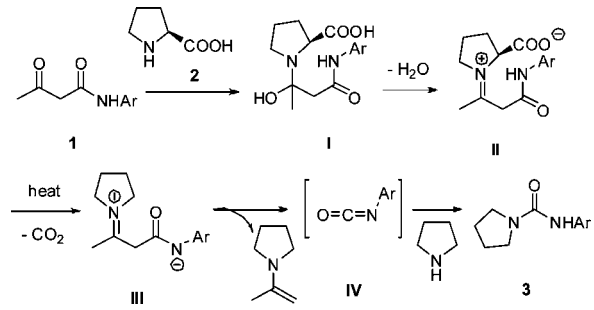
Scheme 3. Reactions of Acetoacetanilides with *O*/*S*-Nucleophiles



NuH = BnOH; PhOH; BnSH; PhSH
amine = TEA or pyrrolidine

To clarify the decarboxylation involved in the reaction leading to urea (Table 2), we performed a control reaction of L-proline with acetophenone in xylene at 130 °C. As a result, distinct decarboxylation was observed.[22] On the basis of all the results described, a possible mechanism for the efficient one-pot transformation into substituted ureas was proposed, as depicted in Scheme 4 (with L-proline as an example). Initially, a nucleophilic addition between amine

Scheme 4. Possible Mechanism for the Formation of Ureas **3**



2 and acetoacetanilide **1** occurrs to give intermediate **I**, followed by the formation of an iminium ion intermediate **II** via the loss of one molecule of water. Then, decarboxylation might take place, giving key intermediate **III**.[22] Finally, an isocyanate intermediate **IV** would be generated via the elimination of acetone enamine,[23] which, in turn, is captured in situ by the pyrrolidine (from the hydrolysis of acetone enamine)[24] nucleophile, giving the aryl urea **3**.[25,26]

In conclusion, we have developed a practical and efficient protocol for the production of substituted ureas by the reactions of acetoacetanilides with various amines via in situ generated isocyanate intermediates. The reaction features readily available starting materials, wide scope, mild conditions, and high efficiency and is phosgene- and catalyst-free. Further work on the synthetic application of the ureas is ongoing in our laboratory.

Acknowledgment. Financial support by NSFC (20972027) and Training Fund of NENU'S Scientific Innovation Project (NENU-STC08013 and STB07007) is greatly acknowledged.

Note Added after ASAP Publication. The graphic in Table 3 was missing in the pdf file of the version published ASAP September 1, 2010; this has been corrected and reposted September 3, 2010.

Supporting Information Available: Experimental details and characterization for all new compounds and crystal structure data (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) CCDC 771468 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(19) All the acetoacetanilide derivatives were either commercially available or prepared according to the procedure reported. See: (a) Zhang, Z.; Zhang, Q.; Sun, S.; Xiong, T.; Liu, Q. *Angew. Chem., Int. Ed.* **2007**, *46*, 1726. (b) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431.

(20) Complex products were observed in the reaction. The lack of the reactivity of *N*-alkyl acetoacetanilides is probably due to their relatively high pK_a values of the N−H.

(21) Other amines such as ethanol amine, aminopyridine, and *t*-butylamine were also tried but led to complex mixtures.

(22) Decarboxylation of α-amino acids proceeds under conditions such as in the presence of ketone catalyst in hydrocarbon solvents like xylene or tetralin. For references, see: (a) Takano, S.; Nishimura, T.; Ogasawara, K. *Heterocycles* **1977**, *6*, 1167. (b) Hashimoto, M.; Eda, Y.; Osanai, Y.; Iwai, T.; Aoki, S. *Chem. Lett.* **1986**, 893. (c) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, *10*, 889.

(23) Mukaiyama, T.; Tokizawa, M.; Nohira, H.; Takei, H. *J. Org. Chem.* **1961**, *26*, 4381.

(24) Actually, a quite large amount of gas bubbles evolved from the reaction of proline with acetoacetanilides, supposed as CO_2 and gaseous acetone.

(25) Obviously, the formation of the iminium ion intermediate **II** facilitates both the decarboxylation and the enamine elimination processes.

(26) We would like to thank the reviewers for valuable comments on the manuscript.