Synthesis of α-Amido Ketones via Organic Catalysis: Thiazolium-Catalyzed Cross-Coupling of Aldehydes with Acylimines

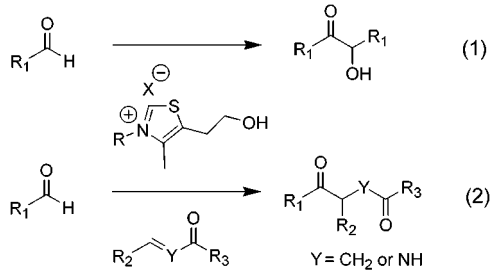
Jerry A. Murry,* Doug E. Frantz,* Arash Soheili, Richard Tillyer, Edward J. J. Grabowski, and Paul J. Reider[1]

Process Research Department
Merck Research Laboratories, Merck and Co. Inc.
P.O. Box 2000, Rahway, New Jersey 07065

Received July 11, 2001

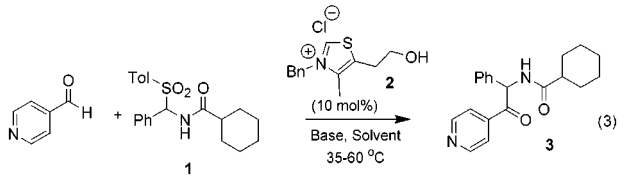
α-Amido ketones are an important class of biologically relevant molecules.[2] Efforts to prepare diverse arrays of these compounds as enzyme inhibitors are current and extensive. In addition, these substrates represent a subclass of building blocks that may be used to make stereochemically complex targets as well as valuable heterocycles.[3] We have been interested in designing nonmetal, organo-catalytic processes toward biologically interesting molecules.[4] In this communication, we disclose a general, practical method for the synthesis of α-ketoamides which utilizes a thiazolium salt to catalyze a cross-coupling reaction of various aldehydes with acylimines.

The use of thiazolium-catalyzed processes to prepare compounds which are the result of an acyl-anion addition reaction have shown general utility in synthetic organic chemistry. The benzoin condensation[5] (eq 1) and the Stetter reaction[6] (eq 2, Y = CH) represent two of the most powerful examples of these types of transformations.



To expand this catalytic methodology toward the synthesis of amido ketones, we envisioned trapping the intermediate thiazolium-stabilized acyl anion with an acylimine (eq 2, Y = NH).[7] There are several potential problems with successfully executing this approach. Most importantly, the acylimine has to be sufficiently reactive to compete with another molecule of aldehyde (benzoin condensation), yet stable enough not to decompose under the reaction conditions or interfere with the thiazolium catalyst. Arylsulfonylamides are stable, readily accessible substrates which can undergo elimination of sulfinic acid to an acylimine under very mild conditions. We envisioned that by employing a tosylamide in a reaction with an aldehyde and a thiazolium salt with a base such as triethylamine, we might be able to effect such a process. We were pleased to find that exposing tosylamide **1** to a mixture of 4-pyridine-carboxaldehyde, a commercially available thiazolium salt **2** and triethylamine provided the desired amido ketone **3** (eq 3).

Table 1. Effects of Solvent and Base on Thiazolium-Catalyzed Addition of Aldehydes to Acylimines



entry	solvent	base	equiv	time	yield **3** (%)
1	THF	TEA	5	24 h	66
2	Toulene	TEA	5	24 h	34
3	DMF	TEA	5	10 h	48
4	CH_3CN	TEA	5	4 h	66
5	CH_2Cl_2	TEA	5	30 min	98
6	CH_2Cl_2	TEA	2	30 min	94
7	CH_2Cl_2	K_2CO_3	5	24 h	75

An initial survey of solvents demonstrated that CH_2Cl_2 is the solvent of choice (Table 1).[8] Furthermore, we found that triethylamine is the optimum base, and we typically employ an excess (5−15 equiv) to ensure complete consumption of the reactants. However, it is possible to use as little as 2 equiv of TEA and achieve complete conversion and good yield (entry 6). Other amine bases such as DBU, tetramethyl guanidine, and DABCO provided little or none of the desired product. However, heterogeneous bases such as potassium carbonate can be utilized, albeit in lower yields (entry 7).

In subsequent investigations, we discovered that the reaction demonstrates wide scope with respect to the aldehyde (eq 4, Table 2). Electron-deficient aldehydes perform much better than their electron-rich counterparts; 3-methoxybenzaldehyde required longer reaction times and higher catalyst loadings relative to the parent compound (entry 11, Table 2). Aliphatic aldehydes (entries 15−16) were also shown to provide the corresponding ketoamides in good yield. We were surprised to find that α,*β*-unsaturated aldehydes were viable substrates (entry 17) and did not undergo 1,4-addition as has been shown for the Stetter process.[6]

The reaction is very tolerant to the amide portion of the tosylamide (entries 1−8), and common amine-protecting groups such as BOC (R_2 = O^{t}Bu) and CBZ (R_2= OBn) could be

(1) We dedicate this paper to Professor David A. Evans on the occasion of his 60th birthday.

(2) (a) Lee, A.; Huang, L.; Ellman, J. *J. Am. Chem. Soc.* **1999**, *121*, 9907−9914. (b) Rano, T. A.; Timkey, T.; Peterson, E. P.; Rotonda, J.; Nicholson, D. W.; Becker, J. W.; Chapman, K. T.; Thornberry, N. A. *Chem. Biol*. **1997**, *4*, 149−155. (c) Marquis, R. W.; Ru. Y.; Yamashita, D. S.; Oh, H. J.; Yen, J.; Thompson, S. K.; Carr, T. J.; Levy, M. A.; Tomaszek, T. A.; Ijames, C. F.; Smith, W. W.; Zhao, B.; Janson, C. A.; Abdel-Meguid, S.; D'Alessio, K. J.; McQueeney, M. S.; Veber, D. F. *Bioorg. Med Chem* **1999**, *7*, 581−588.

(3) Gupta, R. R.; Kumar, M.; Gupta, V. Five-membered Heterocycles. In *Heterocyclic Chemistry*; Springer: Berlin, 1998; Chapter 2.

(4) Recent advances from other laboratories include the use of secondary amines to catalyze Friedel−Crafts, Diels−Alder, 1,3 dipolar cycloaddition and Michael reactions: (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2001**, *123*, 4370−4371. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243−4244. (c) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 9874−9875.

(5) (a) Hassner, A.; Rai, K. M. L. *Comp. Org. Syn*. **1991**, *1*, 541−577. (b) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719−3726. (c) Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241−8242. (d) Chen, Y. T.; Barletta, G. L.; Haghjoo, K.; Cheng, J. T.; Jordan, F. *J. Org. Chem*. **1994,** 59, 7714−7722. (e) White, M. J.; Leeper, F. J. *J. Org Chem*. **2001**, *66*, 5124−5131.

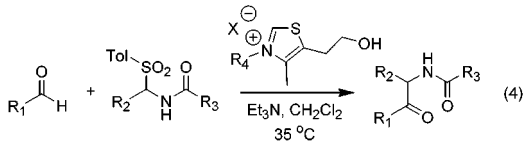
(6) (a) Stetter, H.; Kuhlman, H. *Chem. Ber*. **1976**, 2890−2896. (b) Stetter, H.; Kuhlman, H. *Synthesis.* **1975**, 379−380. (c) Stetter, H. *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 639−712. (d) Harrington, P. E.; Tius, M. A. *Org. Lett*. **1999**, *1*, 649−651. (e) Hempenius, M. A.; Langeveld-Voss, B. M. W.; van Haare, J. A. E. H.; Janssen, R. A. J.; Sheiko, S. S.; Spatz, J. P.; Moller, M.; Meijer, E. W. *J. Am. Chem. Soc*. **1998**, *120*, 2798−2804. (f) Woo, P. W. K.; Hartman, J.; Huang, Y.; Nanninga, T.; Bauman, K.; Butler, D. E.; Rubin, J. R.; Lee, H. T.; Huang, C. C. *J. Labelled Compd. Radiopharm.* **1999**, *42*, 121−127.

(7) (a) Kinoshita, H.; Hayashi, Y.; Murata, Y.; Inomata, K. *Chem. Lett*. 1**993**, 1437. (b) Castells, J.; Lopez-Calahora, F.; Bassedas, M.; Urios, P. *Synthesis* **1988**, 314. (c) Katritzky, A. R.; Cheng, D.; Musgrave, R. P. *Heterocycles* **1996**, *42*, 1, 273.

(8) It should be noted that in entries 1−4, the remainder of the material was starting aldehyde and tosylamide and not decomposition. No further attempt was made to optimize these reactions.

10.1021/ja0165943 CCC: $20.00
Published on Web 09/11/2001

Table 2. Thiazolium Catalyzed Synthesis of Amido Ketones[a]



(4)

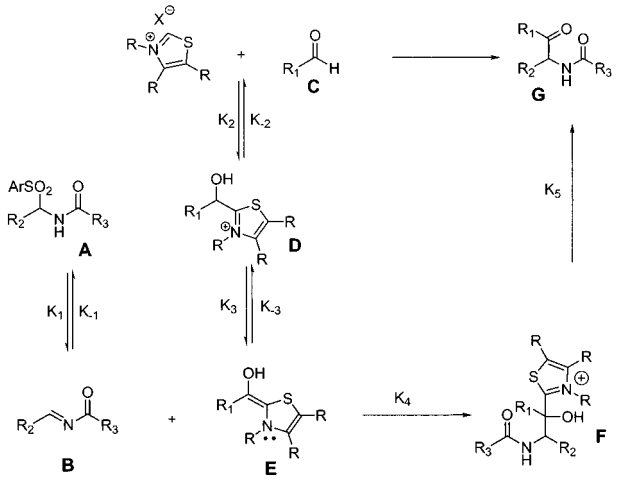
entry[b]	R_1	R_2	R_3	time	yield (%)
1	4-pyridyl	Ph	H	30 min	86
2	4-pyridyl	Ph	CH_3	30 min	93
3	4-pyridyl	Ph	c-C_6H_{11}	30 min	98
4	4-pyridyl	Ph	Ph	30 min	88
5	4-pyridyl	Ph	4-F−Ph	30 min	90
6	4-pyridyl	Ph	4-OMe-Ph	30 min	97
7	4-pyridyl	Ph	OBn	15 min	96
8	4-pyridyl	Ph	O^{t}Bu	15 min	85
9	Ph	Ph	O^{t}Bu	24 h	75
10	2-Br−Ph	Ph	O^{t}Bu	8 h	86
11[c]	3-OMe-Ph	Ph	O^{t}Bu	48 h	68
12	4-CN−Ph	Ph	O^{t}Bu	15 min	80
13	2-furyl	Ph	O^{t}Bu	24 h	73
14	3-pyridyl	Ph	O^{t}Bu	24 h	93
15	CH_3	Ph	O^{t}Bu	24 h	62
16	BnOCH2	Ph	O^{t}Bu	24 h	75
17	PhCH=CH	Ph	c-C_6H_{11}	24 h	80
18	4-pyridyl	4-F−Ph	c-C_6H_{11}	30 min	76
19	4-pyridyl	4-OMe-Ph	c-C_6H_{11}	30 min	84
20	4-pyridyl	c-C_6H_{11}	Ph	24 h	<10
21[d]	4-pyridyl	H	Ph	24 h	58

[a] The reaction was conducted using 1.0 equiv of the tosylamide, 1.1 equiv of the aldehyde, 10 mol % catalyst, and 15 equiv Et_3N in CH_2Cl_2 at 35 °C unless otherwise noted. [b] For entries 1−15 and 18 R_4 = Me. For entries 16 and 17 R_4 = benzyl. [c] Reaction utilized 30 mol % catalyst. [d] K_2CO_3 (5 equiv) was used as the base and THF as solvent.

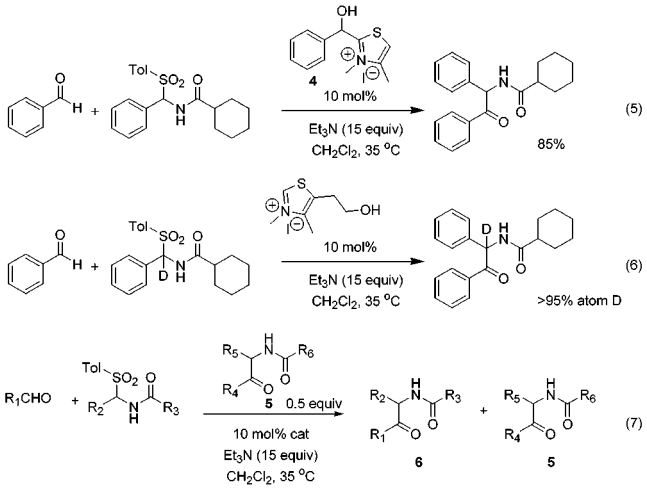
employed (entries 7−16). The electronic nature of the R_2 group of the tosylamide did not seem to have a significant effect on the reaction: 4-F, 4-H, and 4-OMe substitution did not significantly effect the rate or yield of the reaction (entries 3, 18, and 19). Tosylamides derived from aliphatic aldehydes, which have an α-proton, have thus far failed to provide the corresponding ketoamides in good yield (entry 20).[9a] This is presumably due to the known propensity of these substrates to readily isomerize to enamides.[9b] The unsubstituted tosylamide (R_2 = H) provided the desired product, although in moderate yield (entry 21)

At our present level of understanding, we presume that the mechanism is analogous to that proposed for the benzoin condensation and Stetter reaction (Scheme 1).[5b,c,e] Addition of the stabilized ylide to the aldehyde results in intermediate **D** which undergoes deprotonation to the thiazole-enamine **E**. Carbon−carbon bond formation resulting from attack of the enamine to the acylimine followed by catalyst turnover should provide the desired product. In support of this hypothesis, we have identified various intermediates along the reaction pathway. ^{1}H NMR studies confirmed that the sulfonylamide is in equilibrium with the acylimine **B** and triethylammonium sulfinate. Independent synthesis of the presumed intermediate **D**, (**4**, eq 5) was achieved by lithiation of 4-methylthiazole with LDA, quenching with benzaldehyde, and then forming the desired salt with MeI. Subjecting this material to the reaction conditions in catalytic amounts provided the corresponding product in 85% yield (eq 5). We have also found that employing deuterium-labeled tosylamide provided the corresponding product with >95% deuterium incorporation (eq 6) which is consistent with the acylimine operating as an electrophile and encouraging for the possibility of catalytic asymmetric induction. Several crossover experiments were performed by adding a known ketoamide **5** to a unique aldehyde and tosylamide under standard reaction conditions and monitoring the reaction by HPLC (eq 7).

Scheme 1



From these experiments, we were only able to observe ketoamides **5** and **6** and none of the crossover products that would be expected from a reversible process.[10] *In addition, it should be noted that the corresponding benzoin products are not observed and also do not serve as substrates in these reactions.* We presume from these results that the product outcome is under kinetic rather than thermodynamic control.



In summary we have described a general, practical method for the synthesis of keto-amides using a thiazolium-catalyzed cross-coupling of aldehydes with acylimines. We have demonstrated that the process allows for a variety of aldehydes in conjunction with a versatile range of sulfonylamides to provide ready access to structurally diverse α-amido ketones. Further mechanistic studies on this reaction, including elucidation of the rate-limiting step, as well as diastereoselective and catalytic asymmetric variants are currently underway.

Acknowledgment. We thank Pete Dormer for relevant NMR experiments. We also thank Professor Dave Evans and David L. Hughes for fruitful discussions.

Supporting Information Available: General experimental details and characterization of previously undisclosed compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0165943

(9) The corresponding enamide was isolated from the reaction (entry 20) and was identical to that reported in the literature: (a) Couture, A.; Dubiez, R.; Lablache-Combier, A. *J. Org. Chem.* **1984**, *49*, 714−717. (b) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970−8972.

(10) Please consult the Supporting Information for details concerning these experiments.