Facile One-Pot Multicomponent Synthesis of β-Acetamido Ketones with *Amberlyst-15* as Heterogeneous Catalyst[1])

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The one-pot multicomponent coupling of an aromatic aldehyde, an enolizable ketone or keto ester, acetonitrile, and acetyl chloride at room temperature in the presence of *Amberlyst-15* as catalyst affords β-acetamido ketones in high yields. The inexpensive catalyst works under heterogeneous conditions and can be readily reused.

Introduction. – β-Acetamido ketones are useful intermediates in different organic syntheses due to their polyfunctional nature and presence in several bioactive compounds [1]. They can be converted into 3-amino alcohols, which may be applied for the synthesis of various important antibiotics [2]. The multicomponent synthesis of β-acetamido ketones was originally proposed by *Iqbal* and co-workers [3], who used a coupling reaction catalyzed by *Lewis* acids such as $CoCl_2$ [3a–c], polyaniline-supported [$Co(OAc)_2$] [3d], or *Montmorillonite K-10* clay [3e]. This approach is valuable, but the first catalyst requires long reaction times (7 d) at room temperature, and the other two systems only work at elevated temperature (70–80°).

In continuation of our work [4] on the development of useful synthetic methodologies, we herein report that *Amberlyst-15* efficiently catalyzes the one-pot coupling between aromatic aldehydes, enolizable ketones or keto esters, and both acetyl chloride (AcCl) and acetonitrile (MeCN) at room temparature to form β-acetamido ketones (see *Table*).

Results and Discussion. – A series of β-acetamido ketones **1** were prepared from various aromatic aldehydes **2** and acetophenones **3a–h** (R^5 = H; *Table*). The conversion generally furnished the desired product in high yield (78–90%) within 5–7 h. When the propiophenones **3i–k** (R^5 = Me) or the β-keto esters **3l–o** were used as substrates, the reaction yielded a mixture of the *anti*- and *syn*-adducts, as suggested by ^{1}H-NMR spectroscopy. In the case of the propiophenones, the diastereoselectivity was high, the *anti*-configured adduct being the major product. Aromatic aldehydes containing either electron-donating or -withdrawing groups underwent the conversion smoothly. Several functional groups such as halogen (Cl, Br), NO_2, ester, and ether moieties were

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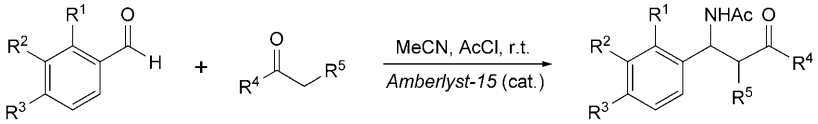
found to be stable under the reaction conditions. The structures of the products were readily established from their ^{1}H-NMR, MS, and elemental-analysis data.

Table. *Synthesis of the β-Acetamido Ketones* **3**



2 **3** **1**

Series	Substituents					Time [h]	Yield [%][a])	*anti/syn*[b])
	R^1	R^2	R^3	R^4	R^5			
a	H	H	H	C_6H_5	H	6.0	89	
b	H	H	Me	C_6H_5	H	6.25	85	
c	H	H	MeO	C_6H_5	H	5.50	86	
d	NO_2	H	H	C_6H_5	H	5.75	85	
e	H	NO_2	H	C_6H_5	H	6.0	78	
f	H	H	NO_2	C_6H_5	H	5.0	90	
g	H	H	H	4-Br–C_6H_4	H	6.25	79	
h	H	H	MeO	4-NO_2–C_6H_4	H	6.0	81	
i	H	H	Me	C_6H_5	Me	7.0	83	87:13
j	H	H	MeO	C_6H_5	Me	6.25	89	79:21
k	H	H	NO_2	C_6H_5	Me	6.50	82	91:9[d]
l	H	H	H	Me	MeOOC	6.0	88	56:44[c])
m	H	H	NO_2	Me	MeOOC	5.25	87	62:38
n	H	H	Cl	Me	EtOOC	5.50	88	66:34[c])
o	H	H	Cl	C_6H_5	EtOOC	5.75	87	73:27

[a]) Isolated yield after chromatographic purification. [b]) Diastereoisomer ratio according to ^{1}H-NMR analysis. [c]) The *anti* isomer was obtained in pure form by crystallization from hexane/AcOEt.

Amberlyst-15 is a commercially available, inexpensive, solid, nonhazardous, heterogeneous acid catalyst and can be easily recovered by filtration. We found that the recovered catalyst can be readily re-used at least three times, basically without loss in catalytic efficiency. For example, in the reaction leading to **1a**, the repeated use of the catalyst gave rise to yields of 89, 85, and 84%. In the absence of the catalyst, no reaction took place.

In conclusion, we have developed a simple, mild, and efficient method for the multicomponent synthesis of β-acetamido ketones using *Amberlyst-15* as a reusable catalyst.

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Experimental Part

General Synthetic Procedure. To a mixture of the aldehyde **2** (1 mmol), the ketone **3** (1 mmol), and AcCl (1 mmol) in MeCN (5 ml), *Amberlyst-15* (200 mg) was added. The mixture was stirred at r.t., and the reaction was monitored by TLC. After completion of the reaction (*ca.* 5–7 h), the mixture was

poured on H_2O (10 ml) and filtered to recover the catalyst. The org. portion was removed from the filtrate, and the remaining mass was extracted with AcOEt (3×10 ml). The extract was concentrated, and the residue was subjected to column chromatography (SiO_2; hexane/AcOEt) to afford the pure product **1**. When keto esters (instead of ketones) were used, the reaction was conducted under N_2 atmosphere. The anal. data of some representative products are given below.

N-*(3-Oxo-1,3-diphenylpropyl)acetamide* (**1a**). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.87 (*d*, *J*=8.0, 2 H); 7.56–7.12 (*m*, 9 H); 5.50 (*m*, 1 H); 3.66 (*dd*, *J*=17.0, 4.5, 1 H); 3.31 (*dd*, *J*=17.0, 5.3, 1 H); 1.89 (*s*, 3 H). FAB-MS: 268 ($[M+H]^+$). Anal. calc. for $C_{17}H_{17}NO_2$: C 76.40, H 6.37, N 5.24; found: C 76.32, H 6.31, N 5.29.

N-*[1-(3-Nitrophenyl)-3-oxo-3-phenylpropyl]acetamide* (**1e**). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.21 (br. *s*, 1 H); 8.10 (*d*, *J*=8.0, 1 H); 7.92 (*d*, *J*=8.0, 2 H); 7.72–7.44 (*m*, 5 H); 7.01 (*d*, *J*=8.5, 1 H); 5.64 (*m*, 1 H); 3.81 (*dd*, *J*=17.0, 4.4, 1 H); 3.48 (*dd*, *J*=17.0, 5.2, 1 H); 2.07 (*s*, 3 H). FAB-MS: 313 ($[M+H]^+$). Anal. calc. for $C_{17}H_{16}N_2O_4$: C 65.39, H 5.13, N 8.97; found: C 65.48, H 5.21, N 8.91.

N-*[2-Methyl-1-(4-nitrophenyl)-3-oxo-3-phenylpropyl]acetamide* (**1k**). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.22 (*d*, *J*=8.0, 2 H); 7.91 (*d*, *J*=8.0, 2 H); 7.67–7.50 (*m*, 5 H); 6.08 (*d*, *J*=8.0, 1 H); 5.41 (*t*, *J*=8.2, 1 H); 4.10 (*m*, 1 H); 2.01 (*s*, 3 H); 1.21 (*d*, *J*=7.0, 3 H). FAB-MS: 327 ($[M+H]^+$). Anal. calc. for: $C_{18}H_{18}N_2O_4$: C 66.26, H 5.52, N 8.59; found: C 66.38, H 5.59, N 8.51.

Ethyl 2-[(Acetylamino)(4-chlorophenyl)methyl]-3-oxobutanoate (**1n**). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.36–7.22 (*m*, 4 H); 6.98 (*d*, *J*=8.9, 1 H); 5.69 (*dd*, *J*=8.9, 5.9, 1 H); 4.21 (*q*, *J*=7.0 2 H); 4.01 (*d*, *J*=5.9, 1 H); 2.19 (*s*, 3 H); 2.04 (*s*, 3 H); 1.28 (*d*, *J*=7.0, 3 H). FAB-MS: 312 ($[M+H]^+$). Anal. calc. for $C_{15}H_{18}ClNO_4$: C 57.79, H 5.78, N 4.49; found: C 57.70, H 5.84, N 4.41.

REFERENCES

[1] J. R. Casimir, C. Turetta, L. Ettouati, J. Paris, *Tetrahedron Lett.* **1995**, *36*, 4797; A. G. Goodfrey, D. A. Brooks, L. A. Hay, M. Peters, J. R. Mc Carthy, D. Mitchell, *J. Org. Chem.* **2003**, *68*, 2623.

[2] K. Kobinata, M. Uramoto, M. Nishii, H. Kusakabe, G. Nakamura, K. Isono, *Agric. Biol. Chem.* **1980**, *44*, 1709.

[3] a) B. Bhatia, M. M. Reddy, J. Iqbal, *J. Chem. Soc., Chem. Commun.* **1994**, 713; b) M. Mukhopadhyay, B. Bhatia, J. Iqbal, *Tetrahedron Lett*. **1997**, *38*, 1083; c) I. N. Rao, E. N. Prabhakaran, S. K. Das, J. Iqbal, *J. Org. Chem.* **2003**, *68*, 4079; d) E. N. Prabhakaran, J. Iqbal, *J. Org. Chem.* **1999**, *64*, 3339; e) D. Bahulayan, S. K. Das, J. Iqbal., *J. Org. Chem.* **2003**, *68*, 5735.

[4] B. Das, J. Banarjee, R. Ramu, R. Pal, N. Ravindranath, C. Ramesh, *Tetrahedron Lett*. **2003**, *44*, 5465; B. Das, J. Banarjee, *Chem. Lett*. **2004**, *33*, 960; B. Das, M. R. Reddy, H. Holla, R. Ramu, K. Venkateswarlu, *J. Chem. Res.* **2005**, 793; B. Das, P. Thirupathi, I. Mahender,V. S. Reddy, Y. K. Rao, *J. Mol. Catal., A* **2006**, *247*, 233.

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