$Zn(ClO_4)_2·6H_2O$ as a Powerful Catalyst for the Conversion of β-Ketoesters into β-Enamino Esters

Giuseppe Bartoli,*[a] Marcella Bosco,[a] Manuela Locatelli,[a] Enrico Marcantoni,[b] Paolo Melchiorre,[a] Letizia Sambri*[a]

[a] Dipartimento di Chimica Organica 'A. Mangini', v.le Risorgimento 4, 40136 Bologna, Italy
Fax +39(051)2093654; E-mail: giuseppe.bartoli@unibo.it

[b] Dipartimento Scienze Chimiche, Università di Camerino, via S.Agostino 1, 62032 Camerino, (Macerata), Italy

Received 8 October 2003

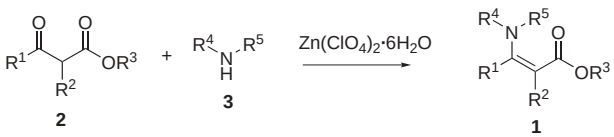
Abstract: $Zn(ClO_4)_2·6H_2O$ proved to be a very powerful catalyst for the condensation of primary and secondary amines with β-ketoesters to give N-substituted β-enaminoesters.

Key words: amino acid derivatives, zinc perchlorate, condensation, amines, keto esters

β-Enamino esters represent an important class of functionalized building blocks. For example, they have proved themselves valuable intermediates for the synthesis of biologically active compounds, such as α-[1] and β-amino acids,[2] γ-aminols,[2b] alkaloids,[3] peptides[4] and heterocyclic derivatives.[5]

These compounds can be obtained via addition of metallic ester or amide enolates to nitriles,[6] tosyl imines,[7] and imidoyl halides,[8] and via addition of enamines[9] or ketimines[10] to activated carboxylic acid derivatives. Moreover, β-enamino esters can be successfully obtained from direct condensation of β-keto esters with amines.[11] Nevertheless, most of the approaches currently available suffer from some limitations, such as low chemical yields and lack of general applicability.

In the last few years, we were interested in the use of metallic perchlorates as Lewis acid promoters in various organic transformations, such as the $LiClO_4$ mediated Friedel–Crafts acylation of activated benzenes[12] and the acylation of alcohols catalyzed by $Mg(ClO_4)_2$.[13] In all cases, best results were obtained using anhydrous perchlorates salts, which showed increased efficiency if warmed under vacuum at 140 °C before use. Owing to the potential hazards connected with the heating of such salts,[14] we focused our attention to more efficient perchlorates, active even in the presence of water. In fact, $Zn(ClO_4)_2·6H_2O$ was recently found to show a catalytic activity superior to $Mg(ClO_4)_2$ for the acylation of alcohols.[15]



Scheme 1

In order to expand the applications of zinc perchlorate, we report here that $Zn(ClO_4)_2·6H_2O$ can act as a powerful catalyst for the synthesis of N-substituted β-enamino esters **1** via condensation of β-ketoesters **2** with primary and secondary amines **3** (Scheme 1).

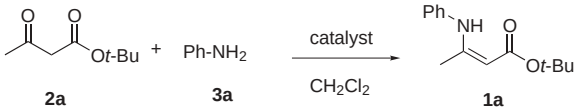
Preliminary results reported in Table 1 showed that in the condensation of *t*-butyl acetoacetate with aniline the catalytic activity of $Zn(ClO_4)_2·6H_2O$ can be enhanced by the presence of anhydrous $MgSO_4$ (Table 1, entry 3 and 4). On the other hand, the reaction is sluggish with $MgSO_4$ alone (Table 1, entry 2).

We found that the best reaction conditions require the presence of a small amount of $Zn(ClO_4)_2·6H_2O$ (5 mol%), dry $MgSO_4$ (30 mol%) and 1.5 equivalents of amine with respect to the β-ketoester at room temperature in CH_2Cl_2. The catalyst is very active, stable to air-moisture and not expensive. In addition, it can be quantitatively recovered by filtration, reactivated by heating in an oven at 60 °C[16] overnight and reused. We repeated this recovering procedure several times and we never observed loss of activity.

The methodology[17] can be applied to cyclic and acyclic β-ketoesters, giving in all cases very good results with primary, secondary, benzylic and aromatic amines.

The reaction suffers from steric hindrance, therefore with acyclic β-ketoesters carrying a substituent different than hydrogen in the α-position or with a bulky amine it is necessary to carry out the reaction at reflux (40 °C).

Table 1 Condensation of *t*-Butyl Acetoacetate **2a** with Aniline **3a** (1.5 equivalents) in CH_2Cl_2 under Various Reaction Conditions



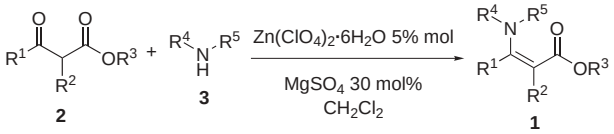
2a **3a** **1a**

Entry	Catalyst (mol%)	Time (h)	Yield (%)
1	–	115	58
2	$MgSO_4$ (30)[a]	115	98
3	$Zn(ClO_4)_2·6H_2O$ (5)	80	98
4	$Zn(ClO_4)_2·6H_2O$ (5), $MgSO_4$ (30)[a]	48	96[b]
5	$Zn(ClO_4)_2·6H_2O$ (5), $MgSO_4$ (30)[a]	21	98

[a] Dried in oven at 60 °C overnight before use.
[b] Reaction carried out with 1 equiv of aniline.

SYNLETT 2004, No. 2, pp 0239–0242
Advanced online publication: 04.12.2003
DOI: 10.1055/s-2003-44974; Art ID: G27003ST

Table 2 Synthesis of β-Enamino Esters **1** via Condensation of β-Keto Ester **2** (1 equivalent) with Amine **3** (1.5 equivalents) in the Presence of $Zn(ClO_4)_2·6H_2O$ (5 mol%) and $MgSO_4$ (30 mol%) at Room Temperature, Unless Otherwise Mentioned



Entry	R^1	R^2	R^3	R^4	R^5	Product	Time (h)	Yield (%)
1	Me	H	*t*-Bu	Chx	H	**1b**	16[a]	71
2	Me	H	*t*-Bu	*n*-Bu	H	**1c**	7	77
3	Me	H	*t*-Bu	*p*-OMe-Ph	H	**1d**	48	95
4	Me	H	*t*-Bu	$-(CH_2)_4-$		**1e**	8	97[b]
5	$-(CH_2)_3-$		Et	Ph	H	**1f**	5	99
6	$-(CH_2)_3-$		Et	*n*Bu	H	**1g**	8	91
7	$-(CH_2)_4-$		Et	Ph	H	**1h**	24	95
8	Et	Me	Et	$PhCH_2$	H	**1i**	16[a]	96[b]
9	C_7H_{15}	Me	Et	$PhCH_2$	H	**1l**	30[a]	97
10	Et	Me	*t*-Bu	$PhCH_2$	H	**1m**	26[a]	77
11	Ph	H	Et	$PhCH_2$	H	**1n**	15[a]	85
12	Me	Cl	Et	Ph	H	**1o**	28	95

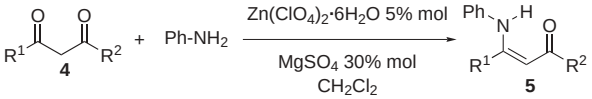
[a] Reaction carried out at reflux.
[b] Reaction carried out with 1 equiv of amine.

Since it has been recently reported[18] that perchlorate salts activate anhydrides forming a cyclic complex, it may be expected that perchlorates are able to activate other 1,3-dicarbonyl compounds, such as β-diketones, to form an electrophilic complex, which undergoes a smooth addition from an aminic nucleophile (Table 2).

To confirm this hypothesis, we applied this methodology to other 1,3-dicarbonyl substrates, such as β-diketones. Preliminary data are reported in Table 3. The obtained results show that the condensation of various β-diketones **4** with aniline proceeds smoothly in high yields in all examined cases. This methodology can be applied to symmetrical β-diketones. In the case of unsymmetrical compounds the regiochemistry is controlled by the more reactive carbonyl group, which undergoes the attack of the amine (Table 3, entry 2). However, in the case of 1,1,1-trifluoro-pentan-2, 4-dione (Table 3, entry 4), the obtained product **5d**[19] derives from the addition of the aniline to the although less reactive carbonyl bound to the methyl group. Very likely, this anomalous result can be ascribed to the fact that in solution the starting material is present in over 95% as the keto-enol tautomer **6d** (Figure 1).[20]

In conclusion, $Zn(ClO_4)_2·6H_2O$ shows a strong catalytic activity in promoting the condensation of amines with 1,3-dicarbonyl substrates. The present method appears to be competitive and in some cases superior to previously

Table 3 Synthesis of β-Enamino Ketones **5** via Condensation of β-Diketones **2** (1 equivalent) with Aniline **3a** (1.5 equivalents) in the Presence of $Zn(ClO_4)_2·6H_2O$ (5 mol%) and $MgSO_4$ (30 mol%) at Room Temperature, Unless Otherwise Mentioned



Entry	R^1	R^2	Product	Time (h)	Yield (%)
1	Me	Me	**5a**	4	95
2	Me	Ph	**5b**	5	98
3	Et	Et	**5c**	5.5	89
4	Me	CF_3	**5d**	28	80
5	Ph	Ph	**5e**	31[a]	78

[a] Reaction carried out at reflux.

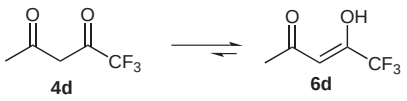


Figure 1

reported procedures. In fact it works with primary, secondary, benzylic and aromatic amines and with various substrates. Moreover, the catalyst is a cheap and easily available reagent, it is stable to air moisture and can be recycled.

Acknowledgment

All work was carried out in the framework of the National Project 'Stereoselezione in Sintesi Organica. Metodologie e Applicazioni' supported by MIUR, Rome, and by the University of Bologna, in the framework of 'Progetto di Finanziamento Pluriennale, Ateneo di Bologna'.

References

(1) (a) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718. (b) Georg, G. I.; Guan, X.; Kant, J. *Tetrahedron Lett.* **1988**, *29*, 403. (c) Felice, E.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1999**, *40*, 4413.

(2) (a) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543. (b) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328. (c) Palmieri, G.; Cimarelli, C. *J. Org. Chem.* **1996**, *61*, 5557. (d) Potin, D.; Dumas, F.; d'Angelo, J. *J. Am. Chem. Soc.* **1990**, *112*, 3483. (e) Cimarelli, C.; Palmieri, G.; Volpini, E. *Synth. Commun.* **2001**, *31*, 2943.

(3) (a) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613. (b) Barta, N. S.; Brode, A.; Stille, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 6201. (c) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org.Chem.* **1994**, *59*, 3575. (d) Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 7001. (e) Blot, J.; Bardou, A.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Célérier, J. P.; Lhommet, G.; Gardette, D.; Gramain, J.-C. *Tetrahedron Lett.* **1997**, *38*, 8511. (f) Michael, J. P.; de Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979. (g) Hernandez, A.; Marcos, M.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 2683. (h) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Haviari, G.; Célérier, J. P.; Lhommet, G.; Gramain, J.-C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122. (i) Michael, J. P.; Parsons, A. S. *Tetrahedron* **1999**, *55*, 10915.

(4) Beholz, L. G.; Benovsky, P.; Ward, D. L.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1997**, *62*, 1033.

(5) (a) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463. (b) Agami, C.; Dechoux, L.; Hebbe, S. *Tetrahedron Lett.* **2002**, *43*, 2521. (c) Stefani, H. A.; de Avila, E. *Synth. Commun.* **2002**, *32*, 2041. (d) Ferraz, H. M. C.; Pereira, F. L. C.; Leite, F. S.; Nunes, M. R. S.; Payret-Arrua, M. E. *Tetrahedron* **1999**, *55*, 10915. (e) Trautwein, A. W.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 8263. (f) Erian, A. W. *J. Prakt. Chem.* **1999**, *341*, 147. (g) Daley, V.; d'Angelo, J.; Cavé, C.; Mahuteau, J.; Chiaroni, A.; Riche, C. *Tetrahedron Lett.* **1999**, *40*, 1657. (h) d'Angelo, J.; Cavé, C.; Desmaele, D.; Gassama, A.; Thominiaux, C.; Riche, C. *Heterocycles* **1998**, *47*, 725.

(6) (a) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833. (b) Lee, A. S.-Y.; Cheng, R.-Y. *Tetrahedron Lett.* **1997**, *38*, 443. (c) Bird, T. G. C.; Olivier, A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 515.

(7) (a) Fukuyama, T.; Yung, Y. M. *Tetrahedron Lett.* **1981**, *22*, 3760. (b) Jiang, N.; Qu, Z.; Wang, J. *Org. Lett.* **2001**, *3*, 2989.

(8) (a) Uneyama, K.; Morimoto, O.; Yamashita, F. *Tetrahedron Lett.* **1989**, *30*, 4821. (b) Fustero, S.; Pina, B.; Simón-Fuentes, A. *Tetrahedron Lett.* **1997**, *38*, 6771. (c) Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Ramirez de Arellano, M. C.; Simón-Fuentes, A. *J. Org. Chem.* **2002**, *67*, 4667. (d) Fustero, S.; Pina, B.; García de la Torre, M.; Navarro, A.; Ramirez de Arellano, M. C.; Simón, A. *Org. Lett.* **1999**, *1*, 977.

(9) (a) Bartoli, G.; Cimarelli, C.; Dalpozzo, R.; Palmieri, G. *Tetrahedron* **1995**, *51*, 8613. (b) Katritzky, A. R.; Fang, Y.; Donkor, A.; Xu, J. *Synthesis* **2000**, 2029.

(10) Fustero, S.; García del la Torre, M.; Jofrè, V.; Pérez Carlon, R.; Navarro, A.; Simón Fuentes, A. *J. Org. Chem.* **1998**, *63*, 8825.

(11) (a) Ferraz, H. M. C.; Oliveira, E. O.; Payret-Arrua, M. E.; Brandt, C. A. *J. Org. Chem.* **1995**, *60*, 7357. (b) Kloek, J. A.; Leschinsky, K. L. *J. Org. Chem.* **1978**, *43*, 1460. (c) Soloshonok, V. A.; Kukhar, V. *Tetrahedron* **1996**, *52*, 6953. (d) Leflemme, N.; Dallemagne, P.; Rault, S. *Synthesis* **2002**, 1740. (e) Calvet, S.; David, O.; Vanucci-Bacqué Fargeau-Bellassoued, M.-C.; Lhommet, G. *Tetrahedron* **2003**, *59*, 6333.

(12) Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* **2002**, *34*, 6331.

(13) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Synlett* **2003**, 39.

(14) (a) Schumacher, J. C. *Perchlorates - their Properties, Manufacture and Uses*; ACS Monograph Series, Reinhold: New York, **1960**. (b) Long, J. *Chem. Health Saf.* **2002**, *9*, 12.

(15) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Sambri, L. *Eur. J. Org. Chem.* **2003**, *6*, 4611.

(16) These conditions are sufficient to reactivate the catalyst, without any decomposition process. $Zn(ClO_4)_2 \cdot 6H_2O$ in fact decomposes under vacuum at temperatures higher than 140 °C.

(17) **Representative Experimental Procedure**: Synthesis of *tert*-butyl-3-anilino-2-butenoate (**1a**). To a round-bottom flask $Zn(ClO_4)_2 \cdot 6H_2O$ (24 mg, 0.063 mmol), $MgSO_4$ (46 mg, 0.38 mmol), *t*-butyl acetoacetate (0.21 mL, 1.26 mmol), CH_2Cl_2 (0.5 mL) and aniline (0.17 mL, 1.90 mmol) were added. The reaction mixture was stirred at r.t. for 21 h. After addition of 5 mL of CH_2Cl_2, the catalyst was filtered off and the solution was concentrated at reduced pressure. The crude product was purified by filtration on a short silica gel column pre-treated with Et_3N. The filtered catalyst was reactivated by heating in a oven at 60 °C overnight and reused. Compounds **5a**, **5b** and **5e** are commercial products. **1f**,[21] **1h**,[21] **1o**,[22] **5c**[23] and **5d**[19] are known compounds. Spectroscopic data for selected examples follow.
***t*-Butyl (*Z*)-3-anilino-2-butenoate (1a):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, 3 × CH_3), 1.97 (s, 3 H, CH_3), 4.60 (bs, 1 H, CH), 7.05–7.20 (m, 3 H, Ph), 7.25–7.35 (m, 2 H, Ph), 10.40 (bs, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2 (CH_3), 28.6 (CH_3), 78.5 (C), 87.8 (CH), 124.2 (CH), 124.6 (CH), 128.9 (CH), 139.5 (C), 158.0 (C), 170.3 (C). IR (nujol): ν_{NH} = 3272 cm^{-1}. MS (EI): *m/z* (%) = 233(6) [M$^+$], 17 7(16), 118 (41), 77 (30), 59 (100).
Ethyl (*Z*)-2-(butylamino)-1-cyclopentene-1-carboxylate (1g): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, 3 H, CH_3, J_{HH} = 7.2 Hz), 1.27 (t, 3 H, CH_3, J_{HH} = 7.2 Hz), 1.35–1.40 (m, 2 H, CH_2), 1.45–1.60 (m, 2 H, CH_2), 1.80–1.90 (m, 2 H, CH_2), 2.45–2.60 (m, 4 H, 2 × CH_2), 3.15–3.25 (m, 2 H, CH_2), 4.13 (q, 2 H, CH_2, J_{HH} = 7.2 Hz), 7.40 (bs, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.6 (CH_3), 14.7 (CH_3), 19.8 (CH_2), 20.8 (CH_2), 28.9 (CH_2), 31.9 (CH_2), 32.9 (CH_2), 44.2 (CH_2), 58.2 (CH_2), 91.9 (C), 164.8 (C), 168.4 (C). IR (neat): ν_{NH} = 3320 cm^{-1}. MS (EI): *m/z* (%) = 211 (43) [M^+], 182 (9), 166 (28), 122 (100).

(18) Chakraborti, A. K.; Sharma, L.; Gulhane, R.; Shivani *Tetrahedron* **2003**, *59*, 7661.

(19) (a) Filyakova, V. I.; Karpenko, N. S.; Kuznetsova, O. A.; Pashkevich, K. I. *Russ. J. Org. Chem.* **1998**, *34*, 381. (b) We confirmed the structure of **5d** with NOE NMR experiments.

(20) Katsuyama, I.; Ogawa, S.; Yamaguchi, Y.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Synthesis* **1997**, 1321.

(21) Naringrekar, V. H.; Stella, V. J. *J. Pharm. Sci.* **1990**, *79*, 138.

(22) Fretz, H.; Gaugler, M.; Schneider, J. *Helv. Chim. Acta* **2000**, *83*, 1145.

(23) Sugita, T.; Eida, M.; Ito, H.; Komatsu, N.; Abe, K.; Suamapp, M. *J. Org. Chem.* **1987**, *52*, 3789.