The reactions of the Betti base with 1,3-dicarbonyl compounds

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Reaction of the Betti base 1-(α-aminobenzyl)-2-naphthol with 1,3-dicarbonyl compounds at room temperature in CH_3OH in the presence of *p*-toluenesulfonic acid leads to the corresponding enamino carbonyl products **3**, in high yield and with high chemical purity. Among them, **3b** was proven to be an enamine with *cis*-configuration by single crystal X-ray diffraction analysis.

Keywords: Betti base 1-(α-aminobenzyl)-2-naphthol, 1,3-dicarbonyl compounds, condensation, X-ray crystal structure

At the beginning of last century, Betti reported the synthesis of 1-(α-aminobenzyl)-2-naphthol (Betti base),[1-5] starting from 2-naphthol, benzaldehyde and ammonia. However, in spite of the ready availability and low cost of this material, the early publications were neglected. Only recently has there been an increasing focus on the Betti base.[6,7] The Betti base and its derivatives have now been successfully applied in organic synthesis.[8-16] As chiral catalysts, cheap resolving agents or optically active ligands. In spite of the two potentially reactive functional groups in the Betti base, relatively few publications have appeared in this field. To the best of our knowledge, there are no reports on the reactions of the Betti base with 1,3-dicarbonyl compounds. Our present aim was to extend the synthetic applicability of the Betti base in the preparation of a new type of Betti base derivative. Herein, we report a simple and convenient procedure for the condensation of Betti base and 1,3-dicarbonyl compounds in the presence of *p*-toluenesulfonic acid (*p*-TSA) in CH_3OH at room temperature.

In our initial search for appropriate reaction conditions, we examined the reaction of Betti base with methyl acetoacetate (**2a**) as a model with a variety of catalysts in CH_3OH at room temperature (Scheme 1, Table 1). As shown in the Table 1, (Table 1, entry 5) the best result was obtained when *p*-TSA was used as the catalyst.

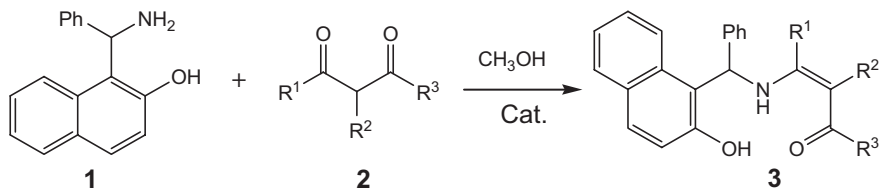
We then examined the reaction in other solvents, such as CH_2Cl_2, THF, ether and toluene. We found that CH_3OH was the best choice. The reactions of different 1,3-dicarbonyl compounds with Betti base in CH_3OH using *p*-TSA as a catalyst at room temperature gave the corresponding products, in many cases, in high yield (Table 2). However, no products were produced when **2g** or **2k** was used as a substrate (entries 7 and 12, in Table 2).

Table 1 Catalytic effect on the reaction of Betti base with methyl acetoacetate

Entry	Catalyst	Time/h	Yield/%
1	H_2SO_4	12	80
2	H_3PO_4	12	74
3	CF_3COOH	12	82
4	CH_3SO_3H	12	84
5	*p*-TSA	6	88

Compounds **3** are assumed to be auxiliary-induced prochiral enamine compounds which might yield the corresponding chiral amino-alcohol after asymmetric hydrogenation. However, they were inert when treated with reducing agents, such as $LiAlH_4$, $NaBH_4$, Na/C_2H_5OH, Zn/AcOH, $H_2/Pd/C$, etc. This unusual phenomenon led us to determine the structure of these compounds by X-ray crystallography.

Compound **3b** (as a typical example of **3**) was readily obtained from Betti base by treatment with ethyl acetoacetate. The crystal was subjected to a single crystal X-ray diffraction



1 **2** **3**

Scheme 1

Table 2 Condensations of Betti base with 1,3-dicarbonyl compounds at room temperature in the presence of *p*-TSA

Entry	Compound **2**	R^1	R^2	R^3	Time/h	Yield/%[a]
1	**a**	Me	H	OMe	6	88
2	**b**	Me	H	OEt	3	95
3	**c**	Me	H	OBu	6	92
4	**d**	Et	H	OMe	12	83
5	**e**	Me	Bn	OEt	18	82
6	**f**	$CH_2CH_2CH_2$	$CH_2CH_2CH_2$	OEt	12	91
7	**g**	Ph	H	OEt	48	ND[b]
8	**h**	Me	H	Me	4	90
9	**i**	Me	H	Ph	6	88
10	**j**	Et	H	Ph	72	71
12	**k**	Ph	H	Ph	48	ND[b]
13	**l**	H	H	Ph	2	95
14	**m**	H	H	Cyclohexyl	2	94

[a]Isolated yield.
[b]No product was detected.

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analysis. The data collection was carried on a Rigaku R-AXIS RAPID diffractometer at 298K. The X-ray structure of compound **3b** is shown in Fig. 1.[17] In the structure of compound **3b**, The bond lengths of C(1)–N(2), N(2)–C(18) and C(18)–C(19) are 1.4675(16) Å, 1.333(2) Å and 1.368(2) Å, respectively, and the bond angles of C(1)–N(2)–C(18), C(18)–C(19)–C(20) are 126.54(10)°, 124.60(16)°, respectively. The atoms N(2), C(18), C(19) are coplanar, shown by the torsion angle N(2)–C(18)–C(19)–C(20) of –2.20 (2)° (Fig. 1 and Table 3). The structure of compound **3b** can be viewed as a conjugated system in which the electrons are delocalised over the atoms N(2)–C(18)–C(19)–C(20)–O(32) (Scheme 2). In the crystal structure, the amino, hydroxy and carbonyl groups are involved in hydrogen bonding. Amino atom N(2) acts as hydrogen-bond donor, *via* atom H(201), to atom O(31) and O(32), forming intramolecular hydrogen bonds. A centrosymmetric hydrogen-bond dimer centred at (0, 1/2, 1/2) is formed by the intermolecular hydrogen bond O(31)–H(301)…O(32)^{i} [Symmetry code: (i) -*x*; -*y* + 1; -*z* + 1] (Table 4 and Fig. 2). All of these probably make it difficult to reduce the compound.

Furthermore, the ^{1}H NMR spectra of compound **3b** revealed that, in $CDCl_3$ solution there was a set of weak signals corresponding to **3b**(**B**) besides the predominant signals corresponding to **3b**(**A**) (Scheme 3, the peak area ratio is about 1:9). The spectra showed a broad singlet at δ 9.63 corresponding to HO group in naphthol, two singlets at δ 6.66, δ 5.69 corresponding to CH of the enamine, which suggest the presence of a chain tautomer **3b**(**B**). However, in DMSO-d_6 solution, compound **3b** existed almost in the form of **3b**(**B**). The ring-chain tautomerism in other derivatives of Betti base is a general feature.[18-20] We concluded that in $CDCl_3$ solution the compound **3b** might exist in a ring-chain tautomeric equilibrium between **3b**(**A**) and **3b**(**B**).

In conclusion, we have developed a simple and convenient method for the synthesis of a new type of Betti base derivatives by treatment of the Betti base with 1,3-dicarbonyl compounds in the presence of *p*-TSA as a catalyst.

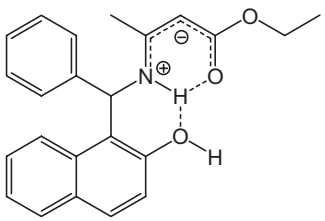
Table 3 Selected bond lengths (Å)

O(31)–C(11)	1.3624 (17)	O(33)-C(21)	1.429 (2)
O(32)–C(20)	1.235 (2)	N(2)–C(1)	1.4675 (16)
O(33)–C(20)	1.350 (2)	N(2)–C(18)	1.333 (2)

Table 4 Hydrogen-bond geometry (Å,°)

D–H…A	D–H	H…A	D…A	D–H…A
O(31)–H(301)…O(32)^{i}	0.93	1.80	2.7182 (15)	170
N(2)–H(201)…O(31)	0.89	2.25	2.8182 (17)	122
N(2)–H(201)…O(32)	0.89	2.11	2.7634 (13)	129

Symmetry code: (i) -*x*; -*y* + 1; -*z* + 1



Scheme 2

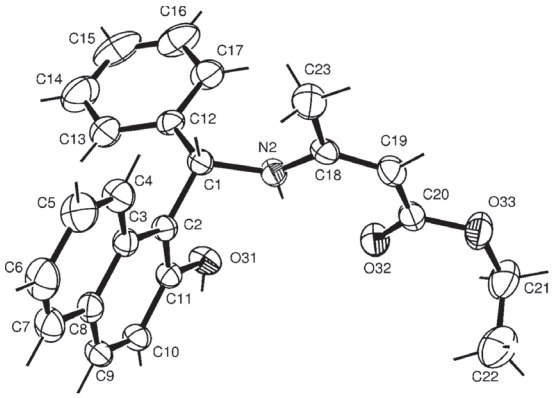


Fig. 1 Molecular structure of compound **3b**.

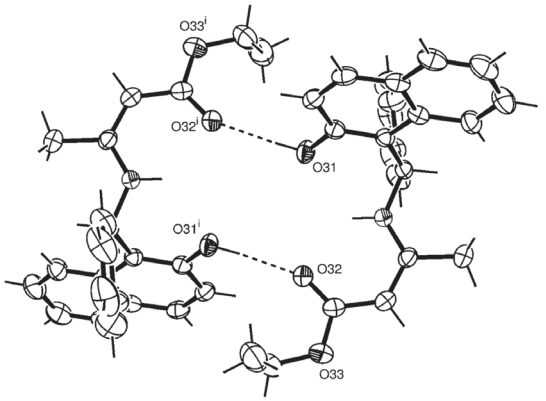


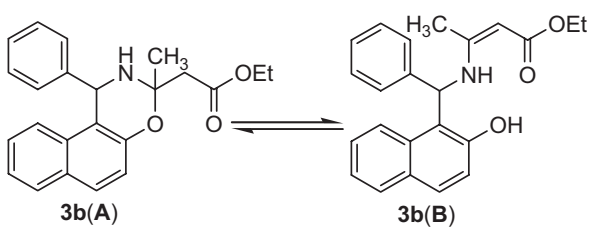
Fig. 2 Partial packing diagram for compound **3b**.

Experimental

Melting points were determined on a Büchi B-540 melting apparatus and are uncorrected. The NMR spectra were measured on a Bruker Advance III 500 or Varian Mercury Plus-400 instrument using DMSO-d_6 or $CDCl_3$ as the solvent with TMS the as the internal standard. IR spectra were recorded using KBr pellets on a Nicolet 6700 FI-IR spectrophotometer. Mass spectra were measured with GCT Premier CAB 075 or Thermo Finnigan LCQ-Advantage (EI). Compound **2j**, **2l**, **2m** were prepared according to the literature.[21-23]

General procedure

The 1,3-dicarbonyl compounds (1.5 mmol) and *p*-TSA (0.1 mmol) were added to a solution of Betti base (1 mmol) in CH_3OH (8 ml). The mixture was stirred at room temperature for the time indicated in Table 2, during which a crystalline product separated out. The resulting mixture was concentrated *in vacuo* to about 3 ml, and the crystalline product was collected by filtration and recrystallised from CH_3OH.



3b(**A**) **3b**(**B**)

Scheme 3

3a: Colourless crystals; m.p. 150–152°C; IR (KBr) cm^{-1}: 3186, 2947, 1617, 1580, 1513, 1443, 1266, 1189, 815; ^1H NMR (400 Hz, $CDCl_3$ main form): δ 7.79–7.70 (m, 11H), 5.68–5.62 (ss, 1H), 3.71–3.68 (ss, 3H), 3.39 (br, 1H), 2.99–2.77 (m, 2H), 1.63–1.60 (ss, 3H); MS *m/z* (%): 347 (M^+, 1), 274 (3), 231 (100), 115 (4), 84 (39); Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.18; H, 5.98; N, 4.11%.

3b: Colourless crystals; m.p. 162–164°C; IR (KBr) cm^{-1}: 3294, 3064, 2978, 1635, 1588, 1518, 1437, 1355, 1261, 1183, 1104, 1053; ^1H NMR (500 Hz, $CDCl_3$ main form): δ 7.74–7.09 (m, 11H), 5.63–5.61 (ss, 1H), 4.16 (q, 2H, J = 7 Hz), 3.37 (br, 1H), 2.94 (d, 1H, J = 15 Hz), 2.79 (d, 1H, J = 15 Hz) 1.63–1.61 (ss, 3H), 1.24 (t, 3H, J = 7 Hz); ^1H NMR (500 Hz, DMSO-d_6): δ 10.31 (s, 1H), 10.08 (br, 1H), 8.08–7.20 (m, 11H), 6.81 (s, 1H), 4.48 (s, 1H), 4.01–4.00 (m, 2H), 2.05 (s, 1H), 1.16 (t, 3H, J = 6.8 Hz); ^{13}C NMR (125 Hz, DMSO-d_6): δ 169.77, 161.53, 153.42, 143.42, 132.33, 130.04, 129.33, 128.74, 127.30, 126.96, 126.15, 123.00, 122.77, 119.51, 118.95, 82.75, 58.05, 52.54, 19.80, 15.05; MS *m/z* (%) 361 (M^+, 1), 315 (13), 231 (100), 129 (5), 85 (8); Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.50; H, 6.34; N, 3.93%; crystal data: (CCDC No. 601099). empirical formula $C_{23}H_{23}NO_3$, Mr = 361.44, crystal size 0.30 × 0.24 × 0.18 mm, crystal system triclinic, space group P ī, Mo *Kα* radiation, a = 9.602(4) Å, α = 100.775(19)°, b = 9.962(5) Å, β = 109.714(14)°, c = 10.899(5) Å, γ = 93.722(18)°, V = 954.9(7) Å^3, Z = 2, D_x = 1.257 g/cm^3, θ = 3.1-27.6°, μ = 0.08 mm^{-1}, λ = 0.71075 Å, T = 298 (1) K, 9527 measured reflections, 4346 independent reflections, 3124 reflections with $I > 2\sigma$ (I), $-12 \le h \le 11$, $-12 \le k \le 12$, $-14 \le l \le 14$, R = 0.0495.

3c: Colourless crystals; m.p. 150–152°C; IR (KBr) cm^{-1}: 3279, 2961, 2863, 1630, 1589, 1515, 1262, 1181, 1113, 1056, 1012, 815; ^1H NMR (500 Hz, $CDCl_3$ main form): δ 7.73–7.06 (m, 11H), 5.68–5.61 (ss, 1H), 4.13–4.08 (m, 2H), 3.34 (br, 1H), 2.95–2.77 (m, 2H), 1.64–1.54 (m, 5H), 1.40–1.32 (m, 2H), 0.88 (t, 3H, J = 7 Hz); MS *m/z* (%) 389 (M^+, 2), 232 (38), 231 (100), 202 (22), 105 (13), 91 (26), 84 (20); Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.98; H, 6.84; N, 3.49%.

3d: Colourless crystals; m.p. 144–146°C; IR (KBr) cm^{-1}: 3423, 3325, 2990, 2852, 1620, 1600, 1394, 1120, 1054; ^1H NMR (400 Hz, $CDCl_3$ main form): δ 7.72–7.08 (m, 11H), 5.69–5.56 (ss, 1H), 3.70–3.67 (ss, 3H), 3.48 (br, 1H), 2.94–2.70 (m, 2H), 1.98–1.87 (m, 2H), 0.98 (t, 3H, J = 8 Hz); MS *m/z* (%):361 (M^+, 1), 315 (4), 238 (61), 231 (100), 115 (3); Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.32; H, 6.25; N, 3.92%.

3e: Colourless crystals; m.p. 126–128°C; IR (KBr) cm^{-1}: 3423, 3328, 2981, 1724, 1621, 1453, 1392, 1244, 1167, 1101, 1051; ^1H NMR (400 Hz, $CDCl_3$ mian form): δ 7.81–7.69 (m, 2H), 7.33–6.93 (m, 14H), 5.70–5.68 (ss, 1H), 4.21–3.97 (m, 2H), 3.42–3.34 (m, 1H), 3.22–2.99 (m, 2H), 2.39 (s, 1H), 1.72–1.59 (ss, 3H), 1.23–0.97 (m, 3H); MS *m/z* (%): 451 (M^+, 24), 360 (15), 314 (8), 231 (100), 219 (48), 202 (63), 144 (47); Anal. Calcd for $C_{30}H_{29}NO_3$: C, 79.80; H, 6.47; N, 3.10. Found: C, 79.95; H, 6.53; N, 3.21%.

3f: Colourless crystals; m.p. 168–169°C; IR (KBr) cm^{-1}: 3325, 2968, 1641, 1580, 1516, 1273, 1163, 1089, 812, 744; ^1H NMR (500 Hz, DMSO-d_6): δ 10.27 (s, 1H), 9.10 (br, 1H), 8.11–7.18 (m, 11H), 6.61 (s, 1H), 4.05 (t, 2H, J = 7 Hz), 2.80–2.37 (m, 4H), 1.78–1.70 (m, 2H), 1.17 (t, 3H, J = 7 Hz); MS *m/z* (%): 387 (M^+,2), 232 (36), 231 (100), 202 (24), 155 (17), 110 (16); Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.54; H, 6.41; N, 3.75%.

3h: Colourless crystals; m.p. 198–200°C; IR (KBr) cm^{-1}: 3423, 3058, 2599, 1595, 1547, 1440, 1322, 1249, 1099, 1025, 976, 816, 751, 694; ^1H NMR (400 Hz, $CDCl_3$): δ 12.33 (s, 1H), 9.77 (s, 1H), 8.04–7.15 (m, 11H), 6.73–6.72 (ss, 1H), 5.02 (s, 1H), 2.10 (s, 3H), 1.99 (s, 3H); MS *m/z* (%): 331 (M^+, 5), 314 (3), 232 (46), 231 (100), 202 (20), 84 (5); Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.88; H, 6.28; N, 4.31%.

3i: Colourless crystals; m.p. 202–204°C; IR (KBr) cm^{-1}: 3416, 3060, 1618, 1533, 1515, 1342, 1282, 1092, 1068, 1030, 822, 806, 737, 718, 696; ^1H NMR (400 Hz, DMSO-d_6): δ 12.59–12.57 (ss, 1H), 10.35 (s, 1H), 7.86–7.23 (m, 16H), 6.94–6.92 (ss, 1H), 5.83 (s, 1H), 2.19 (s, 3H); MS *m/z* (%): 393 (M^+, 1), 376 (2), 232 (37), 231 (100), 202 (23), 160 (24), 84 (11); Anal. Calcd for $C_{27}H_{23}NO_2$: C, 82.42; H, 5.89; N, 3.56. Found: C, 82.30; H, 5.97; N, 3.50%.

3j: Pale yellow colour crystals; m.p. 194–195°C; IR (KBr) cm^{-1}: 3424, 3061, 2973, 1590, 1572, 1531, 1514, 1432, 1343, 1278, 1183, 1059, 880, 691; ^1H NMR (500 Hz, $CDCl_3$): δ 13.02 (s, 1H), 9.69 (br, 1H), 8.11–6.84 (m, 16H), 6.79–6.78 (ss, 1H), 5.77 (s, 1H), 2.60 (q, 2H, J = 7.5 Hz), 1.30 (t, 3H, J = 7.5 Hz); MS *m/z* (%): 407 (M^+, 1), 232 (39), 231 (100), 202 (22), 105 (13); Anal. Calcd for $C_{28}H_{25}NO_2$: C, 82.53; H, 6.18; N, 3.44. Found: C, 82.41; H, 6.27; N, 3.56%.

3l: Pale yellow colour crystals; m.p. 181–183°C; IR (KBr) cm^{-1}: 3416, 3062, 1620, 1530, 1479, 1291, 1066, 1025, 890, 805, 741, 696; ^1H NMR (400 Hz, DMSO-d_6): δ 10.45 (s, 1H), 8.20 (br, 1H), 7.88–7.19 (m, 17H), 6.69–6.66 (ss, 1H), 5.82–5.80 (ss, 1H); MS *m/z* (%): 379 (M^+, 1), 232 (37), 231 (100), 202 (23), 105 (13), 77 (12); Anal. Calcd for $C_{26}H_{21}NO_2$: C, 82.30; H, 5.58; N, 3.69. Found: C, 82.43; H, 5.46; N, 3.72%.

3m: Pale yellow colour crystals; m.p. 190–192°C; IR (KBr) cm^{-1}: 3423, 3061, 2934, 1629, 1513, 1435, 1318, 1281, 1160, 1086, 983, 877, 813, 742, 697; ^1H NMR (400 Hz, DMSO-d_6 main form): δ 11.38–11.33 (dd, 1H, J_1 = 10.4 Hz, J_2 = 12.4 Hz), 10.25 (s, 1H), 7.85–7.15 (m, 11H), 6.53–6.51 (ss,1H), 3.62–3.58 (m, 1H), 2.36–2.06 (m, 4H), 1.77–1.54 (m, 4H); MS *m/z* (%): 357 (M^+,1), 232 (37), 231 (100), 202 (23), 144 (7); Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.71; H, 6.43; N, 3. 87%.

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References

1 M. Betti, *Gazz. Chim. Ital.,* 1900, **30**, 310.
2 M. Betti, *Gazz. Chim. Ital.,* 1901, **31**, 377.
3 M. Betti, *Gazz. Chim. Ital.,* 1901, **31**, 170.
4 M. Betti and C. Speroni, *Gazz. Chim. Ital*., 1901, **31**, 191.
5 M. Betti, *Org. Synth.*, 1929, **9**, 60.
6 C. Cardellicchio, G. Ciccarella, F. Naso, E. Schingaro and F. Scordari, *Tetrahedron: Asymm.*, 1998, **9**, 3667.
7 C. Cardellicchio, G. Ciccarella, F. Naso, F. Perna and P. Tortorella, *Tetrahedron*, 1999, **55**, 14685.
8 I. Szatmári and F. Fülöp, *Curr. Organic Synth.*, 2004, **1**, 155.
9 G. Palmieri, *Tetrahedron: Asymm.*, 2000, **11**, 3361.
10 C. Cimarelli, G. Palmieri and E. Volpini, *Tetrahedron: Asymm.*, 2002, **13**, 2417.
11 D. X.Liu, L.C. Zhang, Q. Wang, C.S. Da, Z.Q. Xin, R. Wang, M.C.K. Choi and A.S.C. Chan, *Org. Lett.*, 2001, **3**, 2733.
12 J. Lu, X.N. Xu, S.Z. Wang, C.D. Wang, Y.Y. Hu and H.W. Hu, *J. Chem. Soc*., *Perkin Trans.*, 2002*,* **1**, 2900.
13 Y. Wang, X. Li and K. Ding, *Tetrahedron: Asymm.*, 2002, **13**, 1291.
14 J.X. Ji, L.Q. Qiu, C.W. Yip and A.S.C. Chan, *J. Org. Chem.*, 2003, **68**, 1589.
15 M. Periasamy, M.N. Reddy and S. Anwar, *Tetrahedron: Asymm.*, 2004, **15**, 1809.
16 X.Y. Wang and Y.M. Dong, *J. Org. Chem.*, 2005, **70**, 1897.
17 J.H. Li and C.P. Lin, *Acta. Cryst E.*, 2006, **62**, o942; CCDC No. 601099.
18 H.E. Smith and N.E. Cooper, *J. Org. Chem.,* 1970, **35**, 2212
19 I. Szatmári, T.A. Martinek, L. Lázár and F. Fülöp, *Tetrahedron,* 2003, **59**, 2877.
20 I. Szatmári, T.A. Martinek, L. Lázár, A. Koch, E. Kleinpeter, K. Neuvonen and F. Fülöp, *J. Org. Chem*., 2004, **69**, 3645
21 B.R. Davis and M.G. Hinds, *Aust. J. Chem.*, 1992, **45**, 865.
22 O. Sezer and O. Anac, *Helv. Chim. Acta*., 1994, **77**, 2323.
23 D.A. May, Jr. and T.D. Lash, *J. Org. Chem.*, 1992, **57**, 4820.