Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: M. Mladenova & M. Bellassoued (1993) A Convenient Synthesis of Aminoacids by $ZnBr_2$ Promoted Reaction of Ketene bis(Trimethylsilyl) Acetals with Aldimines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:6, 725-736

To link to this article: http://dx.doi.org/10.1080/00397919308009832

SYNTHETIC COMMUNICATIONS, 23(6), 725-736 (1993)

A CONVENIENT SYNTHESIS OF AMINOACIDS BY A $ZnBr_2$ PROMOTED REACTION OF KETENE BIS(TRIMETHYLSILYL) ACETALS WITH ALDIMINES

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ABSTRACT: The $ZnBr_2$ promoted addition of ketene *bis*(trimethylsilyl) acetals to aromatic aldimines affords β-arylaminoacids in good to excellent yields. Under the same reaction conditions vinylic ketene *bis*(trimethylsilyl) acetals give exclusively or mainly δ-phenylaminoacids.

The reaction of ketene silyl acetals with imines has been successfully employed[1-11] for the synthesis of aminoesters or lactams. Equimolar amount of an acidic promotor, such as $TiCl_4$[1-5], $ZnBr_2$[4], $SnCl_4$[4], ZnI_2[6], TMSOTf[7], has been required in most of the cases but some examples of the reaction carried out with a catalytic amount of the promotor, TMSOTf[8], phosphonium salts[9], some transition metal (Rh, Co, Ni) compounds[10], FeI_2[11], trithyl hexachloroantimonate[11], were also recently reported.

We wish to report here the results of our study on the addition of ketene *bis*(trimethylsilyl) acetals to aromatic aldimines

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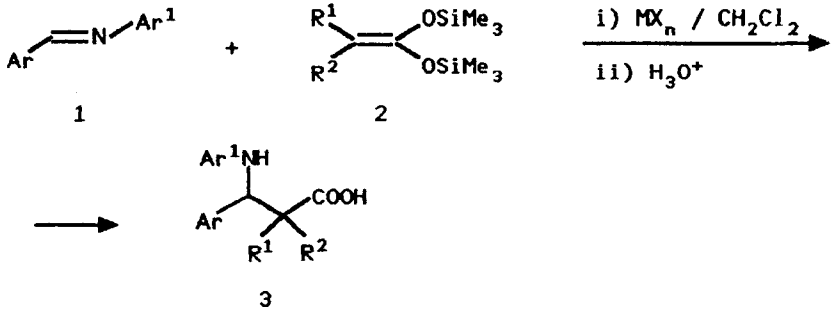
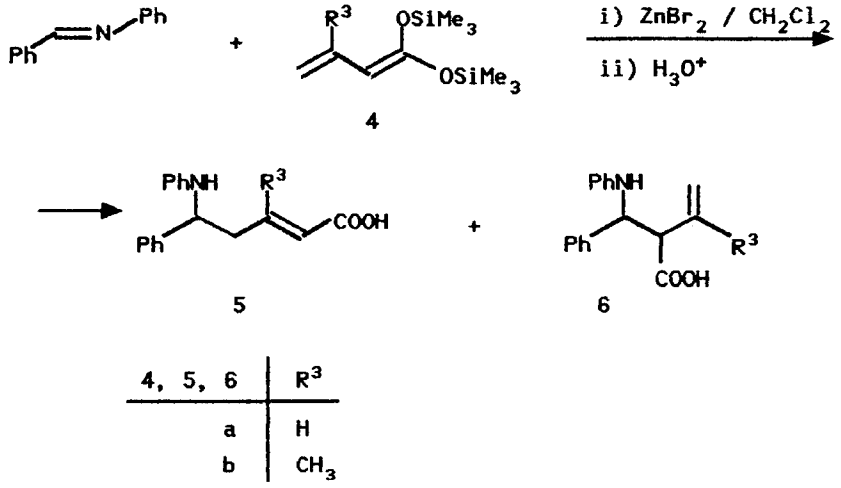
using 10 mol % of a Lewis acid, and a convenient synthesis of β- or δ-arylaminoacids, according to Scheme 1 and 2, when $ZnBr_2$ (10 mol %) is employed as a promotor.

Direct synthesis of aminoacids by addition to Schiff bases of Ivanov[12-14] or Reformatsky[15] reagents of carboxylic acids or their trimethylsilyl esters has already been reported.



For R^1, R^2, Ar and Ar^1 see Table 1.

Scheme 1



4, 5, 6	R^3
a	H
b	CH_3

Scheme 2

Ketene *bis*(trimethylsilyl) acetals have already been employed by Dubois and Axiotis[3] in reaction with aldimines. The direct formation of β-lactams in the presence of an equimolar amount of $TiCl_4$ at room temperature has been reported.

We have found that the reaction (Ar=Ar^1=Ph, R^1=H, R^2=Ph, Scheme 1) promoted by 10 mol % of $TiCl_4$ at -40°C yields in 10 min exclusively the β-phenylaminoacids (syn/anti = 52/48; total yield 45%), no traces of β-lactam being detected in the reaction mixture. This result lead us to screen different promotors and reaction conditions. When after condensation with $TiCl_4$ at -40°C, the reaction mixture was stirred for 24 hrs at room temperature, the diastereomeric ratio was slightly affected (syn/anti = 45/55) without a change in the yield. With $BF_3.Et_2O$ (10 mol %) as a promotor, condensation at -40°C for 10 min produced the diastereomeric mixture syn/anti = 61/39 in 42% yield. A 24 hrs stirring at room temperature after condensation gave syn/anti = 50/50, 43% yield. The use of $ZnBr_2$ afforded much higher yields: 90% yield after 10 min at -40°C and 92% after 24 hrs additional stirring at room temperature, the diastereomeric ratio being in both cases syn/anti = 42/58. A 92% yield was obtained for 15 min at -20°C.

As can be seen, the examined factors do not influence markedly the stereochemistry of the reaction.

On the other hand, the above results show the advantage of $ZnBr_2$ as a promotor of the addition of ketene *bis*(trimethylsilyl) acetals to imines. The possibilities of the proposed method for direct synthesis of β-aminoacids are demonstrated by the series of syntheses shown in Table 1. It is to be noted that the formation of β-lactams was never observed under the conditions used.

In diastereogenious conditions ($R^1 \neq R^2$), the stereoselectivity of the reaction varied from 50/50 to ca. 100%. The relative configuration of the products was established on the basis of the

Table 1. Addition of ketene *bis*(trimethylsilyl) acetals 2 to imines 1 in the presence of $ZnBr_2$ (scheme 1). Reaction conditions: -20°C, 15 min, 1 : 2 : $ZnBr_2$ = 1 : 1 : 0.1.

	Compound				Yield	Isomeric
3	R^1	R^2	Ar	Ar^1	%	ratio
a	CH_3	H	C_6H_5	C_6H_5	84	35/65
b	C_2H_5	H	C_6H_5	C_6H_5	92	40/60
c	C_2H_5	H	4-ClC_6H_4	C_6H_5	70	>95/5
d	C_2H_5	H	C_6H_5	4-$CH_3OC_6H_4$	91	>95/5
e	C_2H_5	H	4-$CH_3OC_6H_4$	C_6H_5	83	90/10
f	i-C_3H_7	H	C_6H_5	C_6H_5	62	88/12
g	C_6H_5	H	C_6H_5	C_6H_5	92	42/58
h	C_6H_5	H	4-ClC_6H_4	C_6H_5	55	59/41
i	C_6H_5	H	3,4(-OCH_2O-)C_6H_3	C_6H_5	78	50/50
j	CH_3	CH_3	C_6H_5	C_6H_5	89	-
k	CH_3	CH_3	C_6H_5	4-ClC_6H_4	72	-
l	CH_3	CH_3	C_6H_5	β-$C_{10}H_7$	73	-
m	CH_3	CH_3	3,4(-OCH_2O-)C_6H_3	C_6H_5	69	-
n	CH_3	CH_3	4-ClC_6H_4	C_6H_5	85	-

coupling constants $J_{2,3}$ of the vicinal methine protons in the methyl esters of 3 prepared with diazomethane, compared to literature data for β-arylaminoesters[10,16-18], as well as to the β-hydroxyesters studied by Jacques et al.[19] which show great similarity in ^{1}H-NMR spectra.

A limitation of our method is that imines derived only from arylamines can be employed. Thus, β-arylaminoacids 3 were obtained in good to excellent yields. When the reaction was tried with benzylidenemethylamine under the same reaction conditions, the formation of neither β-aminoacid nor β-lactam was observed.

The method is not applicable to the first term of the series of 2 (R^1=R^2=H). In this case attempts to carry out the reaction

Table 2. Addition of **4** to PhCH=NPh in the presence of $ZnBr_2$ according to scheme 2 (imine : 4 : $ZnBr_2$ = 1 : 1 : 0.1).

Entry	R^3	t°C	Time min	Compounds obtained Total yield %	Isomeric ratio
1	H	-20	15	95 (**5a** + **6a**)	**5a**/**6a** = 85/15 (in **6a**: M/m = 83/17)
2	H	0	15	85 (**5a** + **6a**)	**5a**/**6a** = 89/11 (in **6a**: M/m = 86/14)
3	CH_3	-20	15	81 (**5b**)	*E*-**5b**/*Z*-**5b** = 80/20

under different conditions failed when $ZnBr_2$, $TiCl_4$, CsF or TBAF were employed.

On the contrary, the reaction proceeded smoothly with the vinylogue **4a** of the first term, as well as with **4b** (Scheme 2, Table 2). The aminoacids were obtained in high yields at -20°C or 0°C. Here again, no product arising from cyclization of aminoacids 5 and 6 was detected in the neutral part of the reaction mixture.

In the case of 1,1-*bis*(trimethylsiloxy)-1,3-butadiene (**4a**), a mixture of γ- and α-addition products with a strong predominance of the linear δ-aminoacid (**5a**/**6a** = 89/11 at 0°C; 85/15 at -20°C) was obtained. The introduction of a methyl group in position 3 increased the regioselectivity of the reaction. Thus, with 3-methyl-1,1-*bis*(trimethylsiloxy)-1,3-butadiene (**4b**), only the product of γ-addition (**5b**) was found in the crude reaction mixture (*E*-**5b** /*Z*-**5b** = 80/20).

It is to be noted that the Reformatsky reaction of trimethylsilyl esters of γ-bromo-α,β-unsaturated acids with benzylideneaniline[15b] is much less regioselective the α-addition product being slightly favoured. The ratio β-lactam/δ-phenylaminoacid is 2:1 in the case of the nonsubstituted crotonate

Table 3. Physical and ^{1}H-NMR data of compounds 3,5 and 6.

Compd	Molecular Formula[a] [Ref.]	Configu-ration [Ref.]	M.p.[b] °C	^{1}H-NMR ($CDCl_3$, TMS), δ (ppm), J (Hz)[c]
3a	[15a]	syn/anti 35/65 [24]	-	1.14(d, 0.65x3H, J=7.0); 1.15(d, 0.35x3H, J=7.2); 2.84(m, 0.65x1H); 3.01(m, 0.35x1H); 4.52(d, 0.65x1H, J=8.2); 4.81(d, 0.35x1H, J=4.7); 6.53-6.64(m,2H); 6.65-6.68(m,1H); 7.04-7.12(m,2H); 7.16-7.34(m,5H).
3b	[15a]	syn/anti 40/60 [25]	-	0.91(t,0.60x3H, J=7.4); 0.92(t,0.40x3H, J=7.3); 1.42-1.55(m,0.40x 1H); 1.59-1.76(m,0.60x1H); 2.63-2.70(m,0.60x1H); 2.73-2.78(m,0.40x x1H); 4.56(d,0.60x1H, J=7.7); 4.70(d,0.40x1H, J=5.5); 6.51-6.56(m, 2H); 6.60-6.69(m, 1H);7.04-7.10(m, 2H); 7.19-7.33(m, 5H).
3c	$C_{17}H_{18}ClNO_2$ (303.79)	anti	175-177	0.73(t, 3H, J=7.3); 1.27-1.35(m, 1H); 1.75-1.80(m, 1H); 3.85-3.88 (m, 1H); 4.53(d, 1H, J=11.2); 7.23-7.37(m, 9H).
3d	[15a]	anti	198-199	[d]0.74(t, 3H, J=7.2); 1.21-1.30(m, 2H); 2.86(m, 1H); 3.62(s, 3H); 4.62(d, 1H, J=9.1); 6.69-7.50(m, 9H).
3e	$C_{18}H_{21}NO_3$ (299.37)	anti	143-144	0.71(t, 3H, J=7.4); 1.32-1.37(m, 1H); 1.78-1.84(m, 1H); 3.79(s, 3H); 3.87(m, 1H); 4.48(d, 1H, J=11.4); 6.82-7.39(m, 9H).
3f	$C_{18}H_{21}NO_2$ (283.37) [15a]	syn [26]	146-147	1.02(d, 3H, J=6.7); 1.07(d, 3H, J=6.9); 2.20-2.30(m, 1H); 2.73(dd, 1H, J=8.6 and 6.1); 4.69(d, 1H, J=8.6); 6.55-6.58(brd, 2H); 6.65 (t, 1H); 7.09(t, 2H); 7.18-7.32(m, 5H).
3g	[12-14], [27]	syn/anti 42/58 [28, 29]	-	3.92(d, 0.42x1H, J=9.5); 3.93(d, 0.58x1H, J=8.9); 4.96(d, 0.42x1H, J=9.5); 4.96(d, 0.58x1H, J=8.9); 6.41-7.61(m, 10H).

3h	[30]	syn/anti 59/41 [30]	-	[e] 3.49(s, 0.59x3H); 3.67(s, 0.41x3H); 3.83(d, 0.51x1H, J=10.0); 3.89(d, 0.41x1H, J=8.2); 4.93(d, 0.59x1H, J=10.0); 4.94(d, 0.41x1H, J=8.2); 6.34-7.43(m, 9H).
3i	$C_{22}H_{19}NO_4$ (361.40)	syn/anti 50/50	-	[e] syn: 3.52(s, 3H); 3.84(d, 1H, J=10.1); 4.90(d, 1H, J=10.1); 5.83(d, 1H, J=1.4); 5.87(d, 1H, J=1.4); 6.59-7.26(m, 8H); anti: 3.69(s, 3H); 3.92 (d, 1H, J=8.1); 4.88(d, 1H, J=8.1); 5.92(d, 1H, J=1.4); 5.95(d, 1H, J=1.4); 6.59-7.26 (m, 8H).
3j	[32]	-	167-168	1.17(s, 3H); 1.28(s, 3H); 4.58(s, 1H); 6.53(d, 2H); 6.63(t, 1H); 7.05 (t, 2H); 7.21-7.32(m, 5H).
3k	$C_{17}H_{18}ClNO_2$ (303.79)	-	180.5-181.5	1.16(s, 3H); 1.28(s, 3H); 4.51(s, 1H); 6.44(d, 2H); 6.99(d, 2H); 7.27 (s, 5H):
3l	$C_{21}H_{21}NO_2$ (319.41)	-	179-181	1.22(s, 3H); 1.32(s, 3H); 4.70(s, 1H); 6.66(d, 1H); 6.93(dd, 1H); 7.10 (dt, 1H); 7.14-7.61(m, 9H).
3m	$C_{18}H_{19}NO_4$ (313.36)	-	186-186.5	1.18(s, 3H); 1.27(s, 3H); 4.48(s, 1H); 5.90(d, 1H, J=1.4); 5.92(d, 1H, J=1.4); 6.53(d, 2H); 6.64(t, 1H); 6.73(s, 1H); 6.77-6.80(m, 2H); 7.07 (t, 2H).
3n	$C_{17}H_{18}ClNO_2$ (303.79)	-	127-128.5	1.16(s, H); 1.28(s, 3H); 4.55(s, 1H); 6.49(brd, 2H); 6.64(t, 1H); 7.07 (t, 2H); 7.25(s, 4H).
5a	$C_{17}H_{17}NO_2$ (267.33) [33]	-	126.5-127	[f] 2.75(brt, 2H, J=7.0); 4.54(t, 1H, J=7.0); 5.93(dt, 1H, J=15.6 and 0.7); 6.51(d, 2H); 6.55(t, 1H); 7.07(m, 1H); 7.10(m, 2H); 7.26-7.36(m, 5H).

(continued)

Table 3. (continued)

Compd	Molecular Formula[a] [Ref.]	Configu-ration [Ref.]	M.p.[b] °C	^{1}H-NMR ($CDCl_3$, TMS), δ (ppm), J (Hz)[c]
5b	$C_{18}H_{19}NO_2$ (281.36) [33]	*E*	146.5-147	[f] 2.22(d, 3H, J=1.2); 2.64(ddd, 2H, J=14.0, 5.6 and 8.9); 4.57(dd, 1H, J=5.6 and 8.9); 5.78(d, 1H, J=1.2); 6.49-7.37(m, 10H).
5b	$C_{18}H_{19}NO_2$ (281.36) [33]	*Z*	115-116	[f] 2.00(d, 3H, J=1.3); 2.42(dd, 1H, J=13.0 and 4.1); 3.65(dd, 1H, J=13.0 and 10.4); 4.60(dd, 1H, J=10.4 and 4.1); 5.92(d, 1H, J=1.3); 6.47-7.47(m, 10H).
6a	$C_{17}H_{17}NO_2$ (267.33)	M[g]	131.5-132	[f] 3.50(dd, 1H, J=7.2 and 7.3); 4.61(d, 1H, J=7.1); 5.14(d, 1H, J=16.2); 5.20 (d, 1H, J=8.8); 5.75-5.93(m, 1H); 6.54-6.72(m, 3H); 7.07-7.30 (m, 7H).

[a] All new compounds gave satisfactory microanalyses.
[b] M.p.s, uncorrected, measured in sealed capillaries.
[c] Recorded on a Bruker WM 250 spectrometer.
[d] Recorded in DMSO-d_6.
[e] ^{1}H-NMR spectra of methyl esters[31].
[f] Recorded on a Bruker AC 200 spectrometer.
[g] Major isomer.

reagent and 3:2 in the case of the β-methyl substituted crotonate reagent. The addition of ketene silyl acetals derived from unsaturated esters to imine complexes of $TiCl_4$ is γ-regioselective and gives the corresponding cyclic products, 5,6-dihydro-2-pyridones, and / or 5-amino-2-alkenoates[1d].

EXPERIMENTAL

All reactions were carried out under dry argon. Dichloromethane was distilled from P_2O_5 and stored over molecular sieve. Anhydrous $ZnBr_2$ was prepared from zinc and 1,2-dibromoethane in THF, then dried *in vacuo* after removal of the solvent.

Ketene *bis*(trimethylsilyl) acetals 2 were prepared according to the Ref. 20 , 1,1-*bis*(trimethylsiloxy)-1,3-butadiene **4a** - according to Ref. 21, and 3-methyl-1,1-*bis*(trimethylsiloxy)-1,3- butadiene **4b** - according to Ref. 22.

Synthesis of arylaminoacids 3, 5 and 6. General procedure:

To a cooled to -20°C solution of 1 (5 mmol) in dichloromethane (5 ml) were consecutively added under stirring at the same temperature anhydrous $ZnBr_2$ (0.5 mmol) and (dropwise) a solution of 2, resp. 4 (5 mmol) in CH_2Cl_2 (5 ml). After additional stirring for 15 min, the cold reaction mixture was poured into 2N HCl and extracted with ether or ethylacetate (depending on the solubility of the product). The organic layer, after washing with water (10 ml) was treated with 4% NaOH to the complete extraction of the acidic product (monitoring by TLC, silica gel, ether/n-hexane 1:1)[23]. The water solution was washed with ether and acidified with conc. HCl to pH ca. 3. The mixture was saturated with NaCl, the acids extracted with ether or ethylacetate and the organic layer was dried over anhydrous $MgSO_4$. The removal of the solvent under reduced pressure afforded the crude aminoacids. Samples for microanalysis were prepared by recrystallization in CH_2Cl_2/n-hexane or $CHCl_3$/n-hexane. In many

cases, to obtain colourless crystals, the solution was shaken with ca. 500 mg silica gel and filtered. Some physical characteristics of the obtained aminoacids are given in Table 3.

REFERENCES AND NOTES

1. a) Ojima, I. and Inaba, S., *Tetrahedron Lett.*, **1980**, 2077, 2081. b) Ojima, I., Inaba, S. and Yoshida, K., *Ibid.*, **1977**, 3643. c) Ojima, I., Inaba, S., and Nagai, M., *Synthesis*, **1981**, 545. d) Brandstadter, S.M., Ojima, I. and Hirai, K., *Tetrahedron Lett.*, **1987**, *28*, 613.
2. Shono, T., Tsubata, K. and Okinaga, N., *J. Org. Chem.*, **1984**, *49*, 1056.
3. Dubois, J.E. and Axiotis, G., *Tetrahedron Lett.*, **1984**, *25*, 2143.
4. Goasdoue, C. and Gaudemar, M., *Tetrahedron Lett.*, ***1985***, ***26***, 1015.
5. Gennari, C., Venturini, I., Gislon, G. and Schimperna, G., *Tetrahedron Lett.*, **1987**, *28*, 227.
6. Colvin, E.W. and McGarry, D.E., *J.Chem.Soc., Chem. Commun*, **1985**, 539.
7. Ikeda, K., Achiwa,K. and Sekiya, M., *Tetrahedron Lett.*, **1983**, *24*, 4707.
8. Guanti, G., Norisano, E. and Banfi, L., *Tetrahedron Lett.*, **1987**, *28*, 4331.
9. Mukaiyama, T., Kashiwagi, K. and Matsui, S., *Chem. Lett.*, **1989**, 1397.
10. Soga, T., Takenoshita, H., Yamada, M. and Mukaiyama, T., *Bull.Chem.Soc.Jpn.*, **1990**, *63*, 3122.
11. Mukaiyama, T., Akamatsu, H. and Han, J.S., *Chem.Lett.*, **1990**, 889; Mukaiyama, T. and Akamatsu, H., Jpn. Kokai, Tokkyo Koho JP 03,275,655 (91,275,655). *C.A.* **1992**, *116*, P 152395j.

12. Kurtev, B. and Robev, St., *Compt.Rend.Acad.Bulg.Sci.*, **1951**, *4*, 373. C.A. **1955**, *49*, 958g.
13. Spassov, A. and Robev, St., *Izv.Acad.Bulg.Sci.*, **1953**, *2*, 53. C.A. **1955**, *49*, 6182i.
14. Marekov, N., Vasilev, G. and Aleksieva, V., *Compt.Rend. Acad.Bulg.Sci.*, **1957**, *10*, 217. C.A. **1958**, *52*, 7243c.
15. a) Bellassoued, M., Arous-Chtara, R. and Gaudemar, M., *J.Organometal.Chem.*, **1982**, *231*, 185; b) El Borgi, A., Bellassoued, M. and Moreau, J-.L., *C.R.Acad.Sci.Paris*, **1988**, *307*, Serie II, 1805.
16. Dardoize, F.,Moreau, J.-L. and Gaudemar, M., *Bull.Soc. Chim.France*, **1973**, 1668.
17. Luche, J.L. and Kagan, H.B., *Bull.Soc.Chim.France*, **1969**, 3500.
18. Spassov, S.L., *Tetrahedron*, **1969**. *25*, 3631.
19. Canceill, J., Basselier, J.J. and Jacques, J., *Bull.Soc. Chim.France*, **1967**, 1024.
20. Ainsworth, C. and Kuo, Y-N., *J.Organometal.Chem.*, **1972**, *46*, 73.
21. Bellassoued, M., Ennigrou, R. and Gaudemar, M., *J.Organometal.Chem.*, **1988**, *338*, 149.
22. Bellassoued, M., Ennigrou, R. and Gaudemar, M., *Ibid.*, **1990**, *393*, 19.
23. The acids **3h** could not be quantitatively extracted with NaOH and were isolated by washing of the solid crude reaction product with n-hexane at room temperature.
24. For the configurations of the corresponding methyl esters see Ref. 10.
25. For the configurations of the methyl esters see Ref. 16.
26. M.p. of the methyl ester prepared with CH_2N_2: 188-189°C (uncorrected, taken on a Kofler hot-stage microscope); lit.[17]:187-188 °C.
27. Kurtev, B. and Mollov, N., *Dokl.Akad.Nouk.SSSR*, **1955**, *101*, 1069; C.A. **1956**, *50*, 3416f.

28, Kurtev, B., Mollov., N., Simova, E. and Stefanovsky, J., *Compt.Rend.Acad.Bulg.Sci.*, **1960**, *13*, 167; C.A.**1960**, *55*, 6437b.

29. For the ^{1}H-NMR spectra of the methyl esters see Ref. 18.

30. Simova, E. and Kurtev, B., *Monatsch.Chem.*, **1965**, *96*, 722.

31. Differences in the chemical shifts and J-constants of the two isomers were observed only in the spectra of the methyl esters of **3h**. The spectra of the corresponding acid isomers coincided. The differences were also better for the methyl esters of **3i** than for the corresponding acids.

32. Holley, A.D, and Holley, R.W., *J.Am.Chem.Soc.*, **1951**, *73*, 3172.

33. The formation of these acids (as mixtures with β-lactams) without any description of the products has been reported[15b].

(Received in UK 28 September, 1992)