5-Isoxazolecarboxaldehyde: A Novel Substrate for Fast Baylis-Hillman Reaction[1]

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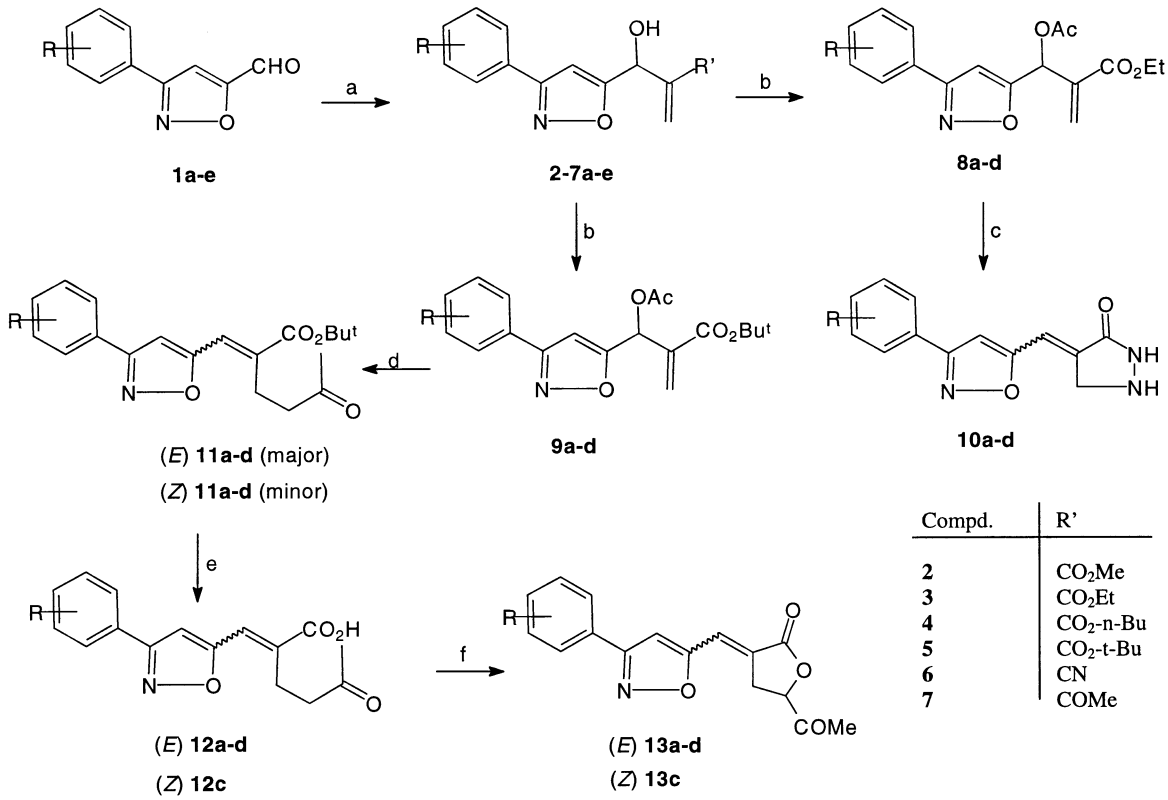
Abstract: 3-Aryl-5-isoxazolecarboxaldehyde undergoes fast Baylis−Hillman reaction with a variety of activated alkenes to yield the corresponding adducts in excellent yields. Some of the Baylis−Hillman adducts reported herein have been subsequently modified to obtain isoxazole substituted pyrazolin-3-ones and γ-butyrolactones.

Key words: 5-isoxazolecarboxaldehyde, Baylis−Hillman reaction, pyrazolin-3-ones, HTIB, γ-butyrolactones

The Baylis−Hillman reaction and its synthetic utility is one of the most attractive and extensively studied subject of recent times.[2] Its importance in solution and solid phase synthetic organic chemistry is enormous as it leads to synthetically useful multifunctional molecules.[2a,3] However, the inherent drawbacks associated with this reaction are the slow reaction rates and limited scope of substrate. To circumvent these shortcomings various alterations in the reaction conditions, both physical and chemical, have been attempted with excellent results.[4] On the other hand, the search for fast reacting electrophiles has led to the identification of diethyl ketomalonate, furfuraldehyde, glyoxalate, 2-cycloalkene-1-ones, etc. as substrates, which all undergo a fast Baylis−Hillman reaction. Indeed, it has also been reported that even simple aldehydes can react very fast either with excess of α,β-unsaturated cycloketones in the presence of $TiCl_4$ or with activated alkenes in presence of DABCO at low temperatures to furnish Baylis−Hillman adducts.[4c,e]

In our efforts directed towards studying the chemical transformations of 3-aryl-5-isoxazolecarboxaldehyde, we observed that these molecules undergo extremely fast Baylis−Hillman reactions under ordinary conditions. Substituted isoxazoles are considered to be one of the most versatile heteroaromatic synthons because they can



Reagents and conditions: (a) CH_2=CHR', DABCO, r.t.; (b) AcCl, pyridine, DMAP (cat.), CH_2Cl_2, r.t.; (c) $NH_2NH_2.H_2O$, MeOH, r.t.; (d) $(CH_3CO)_2CH_2$, K_2CO_3, EtOH, reflux; (e) 20% TFA in CH_2Cl_2, r.t.; (f) HTIB, CH_2Cl_2, r.t.

Scheme

Table 1 Physical Data, Yields[a] and Reaction Times[b,c] of the New Compounds Prepared[d]

Compound	R	R′	Reaction time	Yield (%)	Mp (°C)
2a	H	CO_2Me	15 min	80	64–65
2b	4-Me	CO_2Me	10 min	81	72–74
2c	2-Cl	CO_2Me	20 min	73	oil
2d	4-OBn	CO_2Me	30 min	95	108–110
2e	3-NO_2	CO_2Me	25 min	43	oil
3a	H	CO_2Et	15 min	73	oil
3b	4-Me	CO_2Et	15 min	93	95–96
3c	2-Cl	CO_2Et	15 min	71	oil
3d	4-OBn	CO_2Et	30 min	85	70–2
3e	3-NO_2	CO_2Et	20 min	45	90–92
4a	H	CO_2Bu-*n*	20 min	68	oil
4b	4-Me	CO_2Bu-*n*	15 min	84	88–90
4c	2-Cl	CO_2Bu-*n*	20 min	73	oil
4d	4-OBn	CO_2Bu-*n*	20 min	87	90–92
4e	3-NO_2	CO_2Bu-*n*	25 min	53	101–102
5a	H	CO_2Bu-*t*	20 min	61	78–80
5b	4-Me	CO_2Bu-*t*	15 min	65	155–156
5c	2-Cl	CO_2Bu-*t*	30 min	70	oil
5d	4-OBn	CO_2Bu-*t*	25 min	75	79–80
5e	3-NO_2	CO_2Bu-*t*	30 min	43	110–112
6a	H	CN	15 min	78	74–76
6b	4-Me	CN	15 min	87	54–56
6c	2-Cl	CN	10 min	94	oil
6d	4-OBn	CN	30 min	54	110–111
6e	3-NO_2	CN	30 min	49	oil
7a	H	COMe	15 min	65	oil
7b	4-Me	COMe	15 min	64	oil
7c	2-Cl	COMe	15 min	55	oil
7d	4-OBn	COMe	35 min	60	95–97
7e	3-NO_2	COMe	30 min	41	oil
8a	H	–	5 h	70	68–70
8b	4-Me	–	56 h	69	oil
8c	2-Cl	–	5 h	85	oil
8d	4-OBn	–	7 h	72	94–96
9a	H	–	5 h	75	oil
9b	4-Me	–	5 h	78	38–40
9c	2-Cl	–	5 h	89	108–110
9d	4-OBn	–	7 h	60	82–84
10a	H	–	10 min	63	172–174
10b	4-Me	–	10 min	91	203–205
10c	2-Cl	–	15 min	84	197–199
10d	4-OBn	–	25 min	57	179–180
(*E*)-**11a**	H	–	2 h	67	105–107
(*E*)-**11b**	4-Me	–	2 h	71	69–70
(*E*)-**11c**	2-Cl	–	2 h	70	oil
(*E*)-**11d**	4-OBn	–	2 h	79	112–114
(*Z*)-**11a**	H	–	–	2	oil
(*Z*)-**11b**	4-Me	–	–	3	oil
(*Z*)-**11c**	2-Cl	–	–	10	oil
(*Z*)-**11d**	4-OBn	–	–	2	oil
(*E*)-**12a**	H	–	4 h	91	139–140
(*E*)-**12b**	4-Me	–	4 h	92	174–176
(*E*)-**12c**	2-Cl	–	5 h	95	158–160
(*E*)-**12d**	4-OBn	–	6 h	90	157–158 (dec)
(*Z*)-**12c**	2-Cl	–	22 h	68	oil
(*E*)-**13a**	H	–	20 h	48	153–154
(*E*)-**13b**	4-Me	–	21 h	64	160–162
(*E*)-**13c**	2-Cl	–	16 h	45	140–142
(*E*)-**13d**	4-OBn	–	18 h	54	168–170
(*Z*)-**13c**	2-Cl	–	26 h	36	oil

[a] The reported yields are as obtained after column chromatography.
[b] The reaction time was determined after the addition of aldehyde and reaction carried out as neat.
[c] All data on the basis of 5 mol % of DABCO.
[d] All compounds gave satisfactory chemical analyses; C±0.40, H±0.22, N±0.34.

be efficiently prepared and can be conveniently modified to useful synthetic intermediates.[5] Therefore, in order to explore the synthetic utility of these Baylis–Hillman adducts some of them have been chemically transformed to obtain isoxazole substituted pyrazolin-3-ones and γ-butyrolactones. The results of this study are presented here.

The Baylis–Hillman reaction on 3-aryl-5-isoxazolecarboxaldehyde was realized by adding the aldehydes (**1a–e**) to a pre-stirred (15–20 minutes) mixture of DABCO and activated alkenes (Scheme). Within 10–15 minutes the reaction went to completion as evidenced by TLC (chloroform: ethyl acetate, 8: 2 v/v). The products were isolated in good yields by usual work up procedures and purified by column chromatography (Table 1). In no case was formation of dimerized product observed. Titration studies with respect to the amount of base required for the reaction led to the conclusion that even 1 mol% of base is sufficient to drive the reaction to completion. The change of base from DABCO to DBU yielded similar results.[2h] Since 5-isoxazolecarboxaldehyde is an activated aldehyde, it was considered appropriate to compare the rate of Baylis–Hillman reaction with some other activated aldehyde, such as furfuraldehyde that has been reported[4e] to undergo fast Baylis–Hillman reaction under identical conditions. Indeed it was observed that in comparison to furfuraldehyde, 5-isoxazolecarboxaldehyde shows more than five folds better reactivity under similar reaction conditions. During the studies it was also observed that addition of various solvents influenced the rate of reaction. The best results were obtained when reaction was attempted without solvent followed by DMSO as well as DMF. In a model experiment, the time taken for the quantitative conversion of compound **1b** to product **3b** in the presence of various solvents was determined (Table 2).

In order to study the synthetic utility of these Baylis–Hillman adducts, acetylations of compound **3a–d** and **5a–d** were carried out to obtain the corresponding acetylated derivatives **8a–d** and **9a–d**, respectively. The acetylated products **8a–d** upon reaction with hydrazine hydrate in methanol furnished 1, 2-pyrazolin-3-ones (**10a–d**) within 10 minutes. These compounds were obtained as a mixture of *E*- and *Z*- isomers, which were not separated.

Table 2 Influence[a] of Solvents on the Reaction Time (**1b** to **3b**).

Entry	Solvent	Time
1	Neat	15 min
2	DMSO (2 mL)	45 min
3	DMF (2 mL)	45 min
4	CH_2Cl_2 (2 mL)	3 h
5	MeOH (2 mL)	6 h
6	THF (2 mL)	6.5 h

[a] The comparison was carried out by reacting **1b** (1 mmol) with ethylacrylate (1 equiv) in the presence of DABCO (5 mol %).

In another synthetic strategy, it was envisaged that the reaction of compounds **9a–d** with acetyl acetone could lead to Michael adducts as reported earlier,[6] which could be subsequently cyclized to produce lactones. Accordingly, we carried out reaction of compounds **9a–d** with acetyl acetone in the presence of potassium carbonate in 95% ethanol. This resulted in the formation of products **11a–d**, which were obtained as mixture of *E*- and *Z*- isomers as evidenced on the basis of ^{1}H NMR data.[7] These were separated using column chromatography. The major *E*-isomer was then subjected to acid hydrolysis in presence of 20% TFA in dichloromethane to obtain the (*E*)-acid derivatives **12a–d**. These acids underwent facile cyclization[8] in the presence of hydroxy tosyloxy iodoso benzene (HTIB) to yield the (*E*)-γ-butyrolactone derivatives (**13a–d**). As evident from Table 1, since only compound (*Z*)-**11c** was obtained in satisfactory yield, as a model, adopting the similar synthetic protocol, it was converted to the corresponding (*Z*)-γ-butyrolactone derivative.

In conclusion, our study describes 3-aryl-5-isoxazolecarboxaldehyde as fast reacting substrates for the Baylis–Hillman reaction leading to useful synthetic molecules.

Mps were determined in capillary tubes on a hot stage apparatus containing silicon oil and are uncorrected. IR spectra were recorded on a Perkin–Elmer FTIR spectrophotometer as KBr disc or neat. ^{1}H NMR spectra were recorded on a Bruker Avance DRX-300 or Bruker DPX-200 FT spectrometers, using TMS as an internal reference; chemical shifts (δ) are in ppm and *J* values are in Hz. Mass spectra were recorded on a JEOL JMS-D-300 at 70 eV and the FABMS was recorded on JEOL/ SX-102 spectrometers. Elemental analyses were performed using a Carlo Erba 1108 microanalyzer. R.t. is the temperature range between 20 °C and 35 °C.

Baylis–Hillman Reaction; General Procedure

To a mixture of DABCO (0.056 g, 0.5 mmol) and appropriate alkene (10 mmol) that has been stirred at r.t. for 20 min was added the appropriate aldehyde (**1a–e**) (10 mmol) under stirring and the reaction was allowed to proceed for a period as indicated in Table 1. (Even when all the reactants including aldehyde were mixed simultaneously, the reaction was complete in less than 1 h). Thereafter, 10% HCl (50 mL) was added to neutralize the base, and the reaction mixture was extracted with EtOAc (2 × 100 mL).The organic layers were combined, washed with brine (100 mL), dried (Na_2SO_4), and evaporated under vacuum to yield an oily residue. The residue was purified by column chromatography over silica gel (230–400 mesh) (hexane/EtOAc, 70:30) to yield the adducts as white solids or pale yellow oils.

Acetylation; General Procedure

To a solution of the appropriate compound from **3a–d** or **5a–d** (4 mmol) in dry CH_2Cl_2 (5 mL) was added pyridine (0.38 mL, 4mmol) followed by catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine. To this was added dropwise a solution of acetyl chloride (0.67 mL, 9 mmol) in dry CH_2Cl_2 (3 mL) with stirring at 0 °C. After the addition was complete, the reaction was continued at r.t. for 5–7 h. The excess solvent and pyridine were removed under reduced pressure to afford a residue, which was taken up in EtOAc (100 mL) and H_2O (100 mL). The organic phase was separated, washed with brine (80 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography over silica gel (230–400 mesh) (hexane/EtOAc, 80:20) furnished the acetyl derivatives (**8a–d**, **9a–d**)

Table 3 Spectroscopic Data of Representative Compounds

Product	MS (EI) *m/z* (%)	^{1}H NMR ($CDCl_3$, 200 MHz/ 300 MHz) δ, *J* (Hz)	IR (KBr/Neat) ν (cm^{-1})
2b[a,c]	273 (M^+, 65.3), 212 (30.5), 158 (96.0)	2.39 (s, 3 H), 3.70 (d, 1 H, *J* = 8.0), 3.79 (s, 3H) 5.67 (d, 1 H, *J* = 8.0), 6.02 (s, 1 H), 6.36 (s, 1 H), 7.25 (d, 2 H, *J* = 8.0), 7.58 (d, 2 H, *J* = 8.0)	3369, 1718
3b[a,c]	287 (M^+,14.7), 241 (22.5), 186 (28.6), 160 (40.3), 158 (100)	1.29 (t, 3 H, *J* = 7.0), 2.39 (s, 3 H), 3.73 (d, 1 H, *J* = 8.0), 4.20 (q, 2 H, *J* = 7), 5.67 (d, 1 H, *J* = 8.0), 5.99 (s, 1 H), 6.45 (s, 1 H), 6.56 (s, 1 H), 7.22 (d, 2 H, *J* = 8.0), 7.59 (d, 2 H, *J* = 8.0)	3485, 1708
4b[a,c]	315 (M^+, 13.1), 228 (13.2), 186 (11.0), 167 (72.7), 158 (46.0)	0.89 (t, 3 H, *J* = 7.0), 1.22−138 (m, 2 H), 1.60−1.68 (m, 2 H), 2.39 (s, 3 H), 3.79 (d, 1 H, *J* = 8.0), 4.15 (t, 2 H, *J* = 7.0), 5.73 (d, 1 H, *J* = 7.0), 6.12 (s, 1 H), 6.47 (s, 1 H), 6.50 (s, 1 H), 7.24 (d, 2 H, *J* = 8.0), 7.67 (d, 2 H, *J* = 8.0)	3489, 1706
5b[a,c]	315 (M^+, 11.1), 144 (98)	1.47 (s, 9 H), 2.39 (s, 3 H), 3.71 (d, 1 H, *J* = 8.0), 5.61 (d, 1 H, *J* = 8.0), 5.90 (s, 1 H), 6.38 (s, 1 H), 6.54 (s, 1 H), 7.25 (d, 2 H, *J* = 8.0), 7.60 (d, 2 H, *J* = 8.0)	3305, 1720
6b[a,c]	240 (M^+, 28.6), 189 (14.3), 158 (81.5)	2.40 (s, 3 H), 3.05 (br s, 1 H), 5.53 (s, 1 H), 6.22 (s, 1 H), 6.68 (s, 1 H), 7.27 (d, 2 H, *J* = 8.0), 7.69 (d, 2 H, *J* = 8.0)	3398, 2225
7b[a,d]	257 (M^+, 18.8), 215 (31.8), 186 (42.1), 158 (100)	2.33 (s, 3 H), 2.40 (s, 3 H), 3.78 (d, 1 H, *J* = 8.0), 5.67 (d, 1 H, *J* = 7.0), 6.17, (s, 1 H), 6.56 (s, 1 H), 7.29 (d, 2 H, *J* = 8.0), 7.67 (d, 2 H, *J* = 8.0)	3370, 1669
8b[a,d]	329 (M^+, 15.4), 186 (47.6), 158 (100)	1.27 (t, 3 H, *J* = 7.0), 2.17 (s, 3 H), 2.39 (s, 3 H), 4.22 (q, 2 H, *J* = 7.0), 6.07 (s, 1 H), 6.55 (s, 1 H), 6.56 (s, 1 H), 7.24 (d, 2 H, *J* = 8.0), 7.77 (d, 2 H, *J* = 8.0)	1755, 1722
9c[a,c]	377 (M^+, 2.4), 354 (4.2), 322 (11.0), 216 (23.5), 196 (32.1)	1.45 (s, 9 H), 2.18 (s, 3 H), 5.97 (s, 1 H), 6.48 (s, 1 H), 6.71 (s, 1H), 6.86 (s, 1H), 7.33−7.49 (m, 3 H), 7.70−7.76 (m, 1 H)	1751, 1718
10b[a,c]	255 (M^+, 59.2), 196 (16.1), 158 (100)	(DMSO-d_6) (mixture of E- and Z-isomers): 2.38 (s, 3 H), 2.40 (s, 3 H), 2.57 (m, 4 H), 6.58 (m, 2 H), 7.28−7.34 (m, 4 H, Ar-H), 7.71−7.76 (m, 6 H)	1686
(*E*)-**11c**[b,d]	375 (M^+, 19.6), 321 (14.7), 278 (29.3), 276 (70.6), 232 (16.3)	1.55 (s, 9 H), 2.19 (s, 3 H), 2.71 (t, 2 H, *J* = 7.0), 2.99 (t, 2 H, *J* = 7.0), 6.92 (s, 1 H), 7.36−7.53 (m, 4 H), 7.73−7.73 (m, 1 H)	1710, 1643
(*Z*)-**11c**[b,d]	FABMS 375	1.56 (s, 9 H), 2.19 (s, 3 H), 2.71 (s, 4 H), 6.45 (s, 1 H), 6.91 (s, 1 H), 7.33−7.49 (m, 3 H), 7.69−7.74 (m, 1 H)	1716, 1654
(*E*)-**12c**[a,c]	319 (M^+, 56.7), 278 (37.1), 275 (100)	($CDCl_3$+DMSO-d_6): 2.23 (s, 3 H), 2.81 (t, 2 H, *J* = 7.0), 3.08 (t, 2 H, *J* = 7.0), 7.01 (s, 1 H), 7.37−7.47 (m, 3 H), 7.62 (s, 1 H), 7.72−7.77 (m, 1 H)	1695, 1639
(*Z*)-**12c**[a,d]	319 (M^+, 53.6), 278 (39.7), 276 (100)	2.20 (s, 3 H), 2.79 (s, 4 H), 6.72 (s, 1 H), 7.12 (s, 1 H), 7.33−7.48 (m, 3 H), 7.69−7.73 (m, 1 H)	1699, 1649
(*E*)-**13c**[b,c]	317 (M^+, 34.4), 276 (68.2), 274 (100)	2.35 (s, 3 H), 3.50 (ddd, 1 H, *J* = 3.0, 9.0, 20.0), 3.66 (2dd, 1H, *J* = 3.0, 9.0, 20.0) 4.99 (dd, 1 H, *J* = 5.0, 9.0), 6.99 (s, 1 H), 7.36−7.50 (m, 4 H), 7.72−7.77 (m, 1 H)	1755, 1660
(*Z*)-**13c**[b,d]	317 (M^+, 9.0), 179 (11.8), 178 (100)	2.35 (s, 3 H), 3.25 (ddd, 1 H, *J* = 2.0, 6.0, 16.0), 3.43 (ddd, 1 H, *J* = 2.0, 9.0, 20.0), 4.91 (dd, 1 H, *J* = 6.0, 8.0), 7.05−7.07 (m, 1 H), 7.35−7.52 (m, 3 H), 7.70−7.74 (m, 1 H), 8.02 (s, 1 H)	1766, 1728

[a] 200 MHz
[b] 300 MHz.
[c] KBr.
[d] Neat.

Pyrazolin-3-ones; General Procedure

To the solution of the appropriate compound (**8a−d**) (0.6 mmol) in MeOH (2 mL) was added hydrazine hydrate (0.12 mL, 2.4 mmol) under stirring. As soon as addition was complete, the reaction mixture turned yellow and solid separated out. The product was filtered, washed with H_2O repeatedly and dried. The products were recrystallized from EtOH.

Michael Addition; General Procedure

A mixture of the appropriate compound (**9a–d**) (2.6 mmol), acetylacetone (0.54 mL, 5.2 mmol), K_2CO_3 (0.54 g, 3.8 mmol) in 95% EtOH (20 mL) was refluxed over a water bath for 2 h. The excess of EtOH was removed under reduced pressure and the residue was extracted with EtOAc (2 × 100 mL). The EtOAc layers were combined, dried (Na_2SO_4), and the organic solvent was removed in vacuo. The crude products were purified by column chromatography over silica gel (230–400 mesh) (hexane/EtOAc, 90:10) to yield first the *E*-isomer (major) followed by the elution of *Z*-isomer (minor).

Hydrolysis; General Procedure

To an appropriate compound from (*E*)-**11a-d**, (*Z*)-**11c** (3.3 mmol) was added 20% trifluoroacetic acid (10 mL) in CH_2Cl_2 and the reaction mixture was stirred at r.t. for 6 h. Thereafter, the excess solvent was evaporated and the residue was triturated with hexane to furnish pure acids. These acids were recrystallized from MeOH.

γ-Butyrolactones; General Procedure

To the solution of the appropriate compound from (*E*)-**12a-d** or (*Z*)-**12c** (2.4 mmol) in dry CH_2Cl_2 (15 mL) was added HTIB (0.940 g, 2.4 mmol) and the reaction was stirred at r.t. for 16 h. The reaction mixture was then quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were pooled, dried (Na_2SO_4), and evaporated to obtain a residue. This residue, on filtration through a small band of silica gel, furnished pure γ-butyrolactone derivatives.

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References

(1) CDRI Communication No. **6031**, Indian Patent applied vide application no. NF 399/99 & 400/99.

(2) a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001; and references cited therein.
b) Basavaiah, D.; Muthukumaran, K.; Sreenivasulu, B. *Synthesis* **2000**, 545.
c) Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **2000**, *41*, 2613.
d) Basavaiah, D.; Kumaragurubaran, N.; Padmaja, K. *Synlett* **1999**, 1630.
e) Basavaiah, D.; Krishnamacharyulu, M.; Hyma, R. S.; Sarma, P. K. S.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197.
f) Wei, H. X.; Kim, S. H.; Caputo, T. D.; Purkiss, D. W.; Li, G. *Tetrahedron* **2000**, *56*, 2397.
g) Chamakh, A; M'hirsi, M.; Villieras, J.; Lebreton, J.; Amri, H. *Synthesis* **2000**, 295.
h) Aggarwal, V. K.; Mereu, A. *Chem. Commun*. **1999**, 2311.
i) Mateus, C. R.; Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **2000**, *41*, 2533.
j) Basavaiah, D.; Hyma, R. S.; Muthukumaran, K.; Kumargurubaran, N. *Synthesis* **2000**, 217.
k) Basavaiah, D.; Hyma, R. S.; Padmaja, K.; Krishnamacharyulu, M. *Tetrahedron* **1999**, *55*, 6971.
l) Pringle, W.; Sharpless, K. B. *Tetrahedron Lett.* **1999**, *40*, 5151.
m) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc. A* **2000**, 1331.

(3) Richter, H.; Walk, T.; Holtzel, A.; Jung, G. *J. Org. Chem*. **1999**, *64*, 1362.

(4) a) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539.
b) Rafel, S.; Leahy, J. W. *J. Org. Chem*. **1997**, *62*, 1521.
c) Li, G.; Wei, H. X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett*. **2000**, *41*, 1; and references cited therein.
d) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett*. **2000**, *41*, 2165.
e) Auge, J.; Lubin, N.; Lubineau, A.; *Tetrahedron Lett*. **1994**, *35*, 7947.

(5) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857.
Kozikowski, A. P. *Acc. Chem. Res*. **1984**, *17*, 410.

(6) Bauchat, P.; Le Rouille, E.; Foucaud, A. *Bull. Soc. Chim. Fr*. **1991**, 267.

(7) The *E* and *Z* stereochemistry was assigned on the basis of NOE studies and the protons were assigned on the basis of Hetero Multiple Quantum COSY (HMQC) experiments.

(8) Moriarty, R. M.; Vaid, R. K.; Hopkins, T. E.; Vaid, B. K.; Prakash, O. *Tetrahedron Lett*. **1990**, *31*, 201.

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