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$Cu(OTf)_2$ catalyzed Biginelli type condensation of aldehydes, β-keto esters and carbamates: Synthesis of 3,4-dihydro[1,3]oxazin-2-ones

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$Cu(OTf)_2$ catalyzes effectively a new multicomponent reaction comprising aldehydes, β-ketoester and methyl carbamate in acetonitrile to afford substituted 3,4-dihydro[1,3]oxazin-2-ones in 60-82% yields. These compounds have been found to show inhibition activity against HL-60 cancer cell.

Keywords: Aldehydes, catalysts, multicomponent reaction, copper

The cyclic carbamate oxazinones are a versatile 6-membered heterocyclic ring system present in many biologically important natural products like maystansine, maytanbutine, maystanprine, maytanvaline and colubrinol[1]. In addition, oxazinone derivatives not only exhibit a variety of biological activities such as anti-ulcer, anti-convulsant, penetration enhancer, sedative, analgesic, vasodilator, hypertensive and anti-depressant[2], but also are used as key intermediates in the synthesis of several natural products such as (+)-negamycin[3], L-ristosamine[4]. Literature search revealed that there are various methods for the construction of 1,3-oxazin-2-one moiety[5] available but, to the best of our knowledge, synthesis of 3,4-dihydro[1,3]oxazin-2-ones **2** has not been reported.

In recent years, the search and discovery for new multicomponent reaction on one hand, and the full exploitation of already known multicomponent reactions on the other hand, is therefore of considerable current interest. Recently we have described a simple modification and improvement for Biginelli's three-component cyclocondensation using Lewis acids such as $Cu(OTf)_2$, ref. 6).

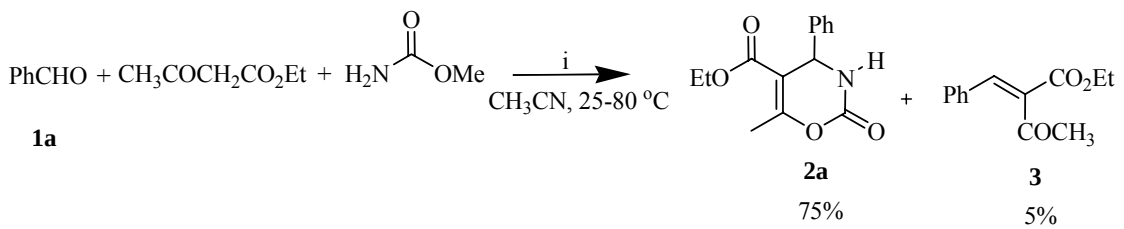
In this paper, $Cu(OTf)_2$ catalyzes a new multicomponent reaction involving aldehydes,β-ketoester and methyl carbamate in acetonitrile to afford substituted 3,4-dihydro[1,3]oxazin-2-ones in high yields.

Results and Discussion

It may be noted that Fe-catalyzed condensation between aldehyde, ethyl acetoacetate and ethyl carbamate failed to cyclize and stops at Mannich adduct[7]. During the course of study on Biginelli reaction, we became interested in subjecting methyl carbamate as one of the components instead of urea. Thus when a mixture containing benzaldehyde, ethyl acetoacetate and methyl carbamate was subjected to react in the presence of $Cu(OTf)_2$ in catalytic amount in CH_3CN, 3,4-dihydro[1,3]oxazin-2-one **2a** was formed in 75% yield (**Scheme I**).

The results for the three-component reaction leading to synthesis of 3,4-dihydro[1,3]oxazin-2-one **2a** using benzaldehyde, methyl carbamate and ethyl acetoacetate catalyzed by Lewis acids are presented in **Table I**.

When other Lewis acid catalysts such as $La(OTf)_3$, $LaCl_3$, $InCl_3$ and $FeCl_3$ were employed, Knoevenagel



1a **2a** 75% **3** 5%

Scheme I — (i) $Cu(OTf)_2$ (1 mole %), CH_3CN, 25°C, 6 hr; followed by heating at 80°C, 6 hr, 75%.

condensation product **3** as side product in considerable quantity was obtained; whereas reactions performed with $Cu(OTf)_2$ produced dihydro[1,3]-oxazin-2-one **2a** exclusively in excellent yield. Among various solvents screened (CH_2Cl_2, $CHCl_3$, benzene, CH_3CN, THF, dioxane and EtOH) best results were obtained with acetonitrile.

Table I — Cu-catalyzed condensation of benzaldehyde, ethyl acetoacetate and methyl carbamate[a]

No.	Lewis acid catalyst	catalyst mole%	solvent	yield of **2a** (%)[b]	yield of **3** (%)
1	None	—	CH_3CN	00	00
2	$Cu(OTf)_2$	1	CH_3CN	75	05
		1	—	00	10
		1	THF	53	10
		1	EtOH	70	10
		1	H_2O	05	10
3	$La(OTf)_3$	5	CH_3CN	50	25
4	$LaCl_3$	5	CH_3CN	35	30
5	$InCl_3$	5	CH_3CN	40	18
6	$FeCl_3$	5	CH_3CN	20	40

[a] Reaction conditions: benzaldehyde (2 mmole), methyl carbamate (2 mmole), ethyl acetoacetate (2 mmole), 25-80°C, 6 hr.
[b] Isolated yield after chromatographic purification.

A variety of aldehydes underwent this multi-component reaction to afford the corresponding 3,4-dihydro[1,3]oxazin-2-ones **2a-i** in good to excellent yields. For example, several aromatic aldehydes were examined under the optimized conditions using 1 mole % of $Cu(OTf)_2$ and the results are shown in **Table II**.

Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents including hydroxy groups reacted efficiently giving products **2a-i** in excellent yields.

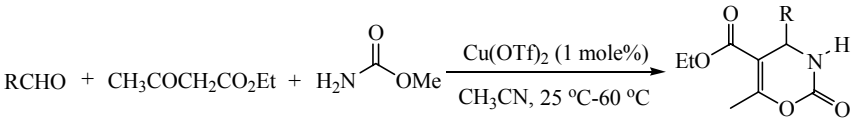
The structure of 3,4-dihydro[1,3]oxazin-2-ones **3a** was confirmed by X-ray analysis (**Figure 1**).

The mechanism of this multi-component reaction is believed to involve, at first, the formation of activated acylimine **4** so that addition of enolate **5** is facilitated to afford the intermediate **3**, which enolizes and then undergoes facile condensation to give 3,4-dihydro-[1,3]oxazin-2-ones **2** (**Figure 2**) [the formation of **3** was confirmed by isolating and characterizing it by spectroscopic techniques such as NMR, IR, etc].

Biological activity (High-throughput screening)

In preliminary studies on biological testing, various 1,3 oxazin-2-ones **2a-i** were screened for inhibition activity studies. When the inhibition activity experiment on HL-60 cancer cell line was carried out, it was found that cell morphology is changing and aggregating including death of a cell. It induced apoptosis in cell culture. The data on percentage of inhibition of growth on HL-60 cancer cell that

Table II — $Cu(OTf)_2$-catalyzed synthesis of 3, 4-dihydro[1, 3]oxazin-2-ones (2a-i)[a]



1(a-i) **2(a-i)**

Compd	R	Time (hr)	Yield of 2[b] (%)
a	Ph	6	75
b	4-Cl-C_6H_4	6	60
c	2-HO-C_6H_4	6	76
d	4-O_2N-C_6H_4	12	62
e	3- O_2N-C_6H_4	12	67
f	4-NC-C_6H_4	12	72
g	3,4-$(MeO)_2$-C_6H_3	6	75
h	3,4-(O-CH_2-O)-C_6H_3	6	80
i	4-F_3C-C_6H_4	6	82

[a] Reaction conditions: aldehyde (2 mmole), methyl carbamate (2 mmole), ethyl acetoacetate (2 mmole), $Cu(OTf)_2$ (1 mole%), 25-80°C, 6 hr.
[b] Isolated yield after chromatographic purification.

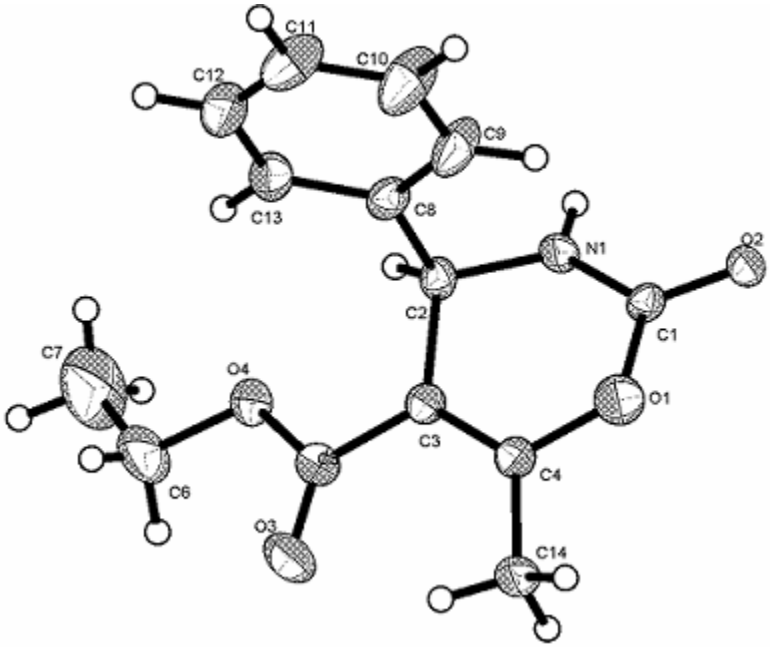
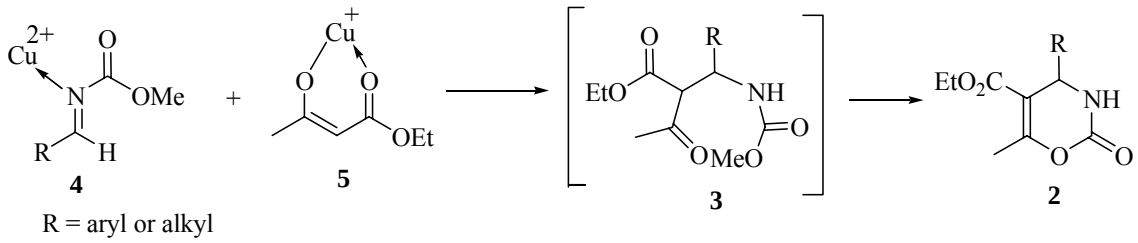


Figure 1 — Single X-ray crystal structure of 1,3-oxazin-2-one **2a**



R = aryl or alkyl

Figure 2 — Cu^{2+}- activation in three-component coupling reaction

Table III — Percentage inhibition by Oxazinones of fully grown culture[a].

Compd	Concentration (% Inhibition) 62.5 µg/mL	125 µg/mL
2a	56.48	57.84
2b	33.07	20.78
2c	76.86	54.78
2d	50.43	60.68
2e	54.09	75.91
2f	45.8	45.57
2g	24.43	47.5
2h	71.48	75.11
2i	62.95	62.86

[a]Fully grown culture = 134×10^4 cells/mL = 100% growth.

occurred with various oxazinones are shown **Table III**.

Conclusion

In conclusion, , a simple three-component coupling reaction is developed for the first time for the synthesis of 3,4-dihydro[1,3]oxazin-2-ones **2** using $Cu(OTf)_2$ as catalyst,. The catalytic system is very effective for the variety of aldehydes **1** to give the corresponding 3,4-dihydro[1,3]oxazin-2-ones **2** in excellent yields.

Experimental Section

General procedure for the preparation of 3,4-dihydro[1,3]oxazin-2-ones, 2a-i

A 25 mL RB flask was charged with aromatic aldehyde **1a-i** (2 mmole), methyl carbamate (0.120 g, 2 mmole), ethyl acetoacetate (0.260 g, 2 mmole), $Cu(OTf)_2$ (7 mg, 1 mole %) and acetonitrile (5 mL). The resulting reaction-mixture was stirred at room temperature for 3 hr and then heated at 80°C for 3 more hr. After the reaction was complete (monitored by TLC), the reaction-mixture was cooled to 25°C and was diluted with ethyl acetate (10 mL)

and washed with water followed by brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude products, which were purified by column chromatography on silica gel using petroleum ether as eluent to afford the pure 3,4-dihydro-[1,3]oxazin-2-ones **2a-i**.

Ethyl 3,4-dihydro-6-methyl-2-oxo-4-phenyl-2*H*-1,3-oxazine-5-carboxylate, 2a

Recrystallized from EtOH. Yield 75%, colourless solid, m.p. 199-201ºC; IR (KBr): 618, 662, 698, 758, 825, 1026, 1090, 1220, 1377, 1459, 1647, 1700, 1724, 2252, 2854, 2925, 3104, 3244, 3395 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.76 (t, *J* = 6.00 Hz, 3H), 1.92 (s, 3H), 3.63 (q, *J* = 7.00 Hz, 2H), 4.89 (d, *J* = 4.00 Hz, 1H), 6.89 (m, 5H), 8.66 (brs, 1H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 14.04, 17.83, 54.66, 59.44, 126.74, 127.48, 128.58, 145.38, 148.58, 152.88, 165.74. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.33; H, 5.71; N, 5.29%.

Ethyl 4-(4-chlorophenyl)-3,4-dihydro-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate, 2b

Recrystallized from EtOH. Yield 60%, colourless solid, m.p. 209-10ºC; IR (Neat): 668, 750, 863, 929, 1041, 1097, 1215, 1242, 1299, 1369, 1446, 1488, 1504, 1643, 1698, 2400, 2898, 3019, 3234 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.18 (t, *J* = 7.05 Hz, 3H) 2.34 (s, 3 H), 4.09 (q, *J* = 7.2 Hz, 2H), 5.28 (d, *J* = 1.17 Hz, 1H), 6.72 – 6.78 (d, *J* = 8.09 Hz, 4H), 8.20 (brs, 1H); ^{13}C NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 13.39, 17.45, 53.90, 58.77, 100.10, 106.33, 107.04, 119.04, 129.80, 137.93, 145.94, 146.78, 152.37, 165.02. Anal. Calcd for $C_{14}H_{14}ClNO_4$: C, 56.86; H, 4.77; N, 4.74. Found: C, 56.85; H, 4.72; N, 4.73%.

Ethyl 3,4-dihydro-4-(2-hdroxyphenyl)-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate, 2c

Recrystallized from EtOH. Yield: 76%; grey colour solid, m.p. 159-63ºC; IR (KBr): 667, 755, 875, 911, 1031, 1091, 1193, 1216, 1237, 1330, 1372, 1460, 1491, 1604, 1651, 1687, 2401, 2928, 3019, 3228, 3324 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.18 (t, *J* = 7.0 Hz, 3H), 2.29 (s, 3H), 3.98 (q, *J* = 7.0 Hz, 2H), 4.43 (s, 1H), 5.53 (s, 1H), 6.64–7.07 (m, 4H), 8.86 (s, 1H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 14.1, 17.8, 23.9, 54.0, 59.2, 83.5, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 64.64; H, 5.45; N, 5.05. Found: C, 64.63; H, 5.41; N, 5.00%.

Ethyl 3,4-dihydro-6-methyl-4-(4-nitrophenyl)-2-oxo-2*H*-1,3-oxazine-5-carboxylate, 2d

Recrystallized from EtOH. Yield: 62%; yellow colour solid; m.p. 175-77ºC; IR (KBr): 757, 890, 928, 1046, 1090, 1220, 1270, 1350, 1450, 1522, 1682, 1710, 2414, 3020, 3200, 3332 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.12 (t, *J* = 7.20 Hz, 3H), 2.30 (s, 3H), 4.00 (q, *J* = 7.07 Hz, 2H), 5.46 (d, *J* = 3.10 Hz, 1H), 7.49 – 7.60 (q, *J* = 7.88 Hz, 1H), 7.70 – 7.75 (d, *J* = 7.80 Hz, 1H), 8.09 – 8.13 (d, *J* = 8.08 Hz, 2H), 8.80 (brs, 1H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 14.4 18.5, 55.6, 60.8, 100.3, 127.7, 128.1, 128.9, 145.2, 148.9, 157.8, 165.5. Anal. Calcd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.83; H, 4.55; N, 9.10%.

Ethyl 3,4-dihydro-6-methyl-4-(3-nitrophenyl)-2-oxo-2*H*-1,3-oxazine-5-carboxylate, 2e

Recrystallized from EtOH. Yield: 67%; yellow colour solid; m.p. 169-70ºC; IR (KBr): 669, 692, 755, 900, 928, 1045, 1091, 1215, 1265, 1316, 1349, 1455, 1526, 1690, 1708, 2400, 3020, 3219, 3326 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.19 (t, *J* = 7.46 Hz, 3H), 2.38 (s, 3H), 4.08(q, *J* = 7.07 Hz, 2H), 5.46 (d, *J* = 3.16 Hz, 1H), 7.46 – 7.57 (q, *J* = 7.84 Hz, 1H), 7.69 – 7.73 (d, *J* = 7.71 Hz, 1H), 8.09 – 8.13 (d, *J* = 8.08 Hz, 2H), 8.79 (brs, 1H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 14.2 18.2, 55.0, 60.2, 99.0, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 166.8. Anal. Calcd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.83; H, 4.55; N, 9.10%.

Ethyl 3,4-dihydro-4-(4-cyanophenyl)-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate, 2f

Recrystallized from EtOH. Yield: 72%; dark brown colour solid; m.p. 190-93ºC; IR (KBr): 668, 698, 758, 847, 962, 981, 1038, 1094, 1215, 1287, 1377, 1458, 1599, 1637, 1687, 2140, 2400, 2855, 2926, 3019, 3245, 3308 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.10 (t, *J* = 7.0 Hz, 3H), 2.20 (s, 3H), 4.0 (q, *J* = 7.2 Hz, 2H), 5.30 (d, *J* = 3.0 Hz, 1H), 7.53 (dd, *J* = 6.9, 2.1 Hz, 2H), 8.25 (dd, *J* = 6.8, 2.0 Hz, 2H), 9.30 (s, 1H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 14.2, 18.0, 53.2, 60.2, 98.0, 116.2, 128.1, 128.3, 131.4, 142.1, 149.2, 153.7, 164.3. Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.83; H, 4.95; N, 9.76%.

Ethyl 3,4-dihydro-4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate, 2g

Recrystallized from ^{i}PrOH. Yield: 75%; colourless solid; m.p. 179-82ºC; IR (Neat): 759, 881, 1008, 1095, 1170, 1229, 1293, 1322, 1364, 1460, 1650, 1701, 2856, 2925, 2954, 3110, 3234 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.15 (t, J = 7.2 Hz, 3H), 2.27 (s, 3H), 4.10 (q, J = 7.2 Hz, 2H), 5.00 (d, J = 3.0 Hz, 1H), 5.90 (s, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 8.89 (brs, 1H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 15.8, 18.4, 54.3, 60.2, 99.8, 101.3, 107.8, 108.4, 102.0, 139.2, 147.3, 148.2, 149.0, 156.0, 164.7. Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 60.08; H, 5.93; N, 4.27%.

Ethyl 4-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate, 2h

Recrystallized from EtOH. Yield: 80%; grey colour solid; m.p. 184-86ºC; IR (KBr): 668, 757, 864, 954, 1012, 1091, 1170, 1216, 1290, 1322, 1367, 1422, 1462, 1490, 1575, 1646, 1704, 2980, 3019, 3115, 3240 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.09 (t, J = 7.00 Hz, 3H), 2.23 (s, 3H), 3.94 (q, J = 7.2 Hz, 2H), 5.18 (d, J = 3.14 Hz, 1H), 5.90 (s, 2H), 6.74 (m, 3H), 8.92 (brs, 1H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 12.75, 16.75, 52.91, 58.31, 98.50, 105.22, 107.18, 115.83, 119.20, 127.04, 131.33, 142.42, 147.03, 151.51, 164.33; Anal. Calcd for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.00; H, 4.91; N, 4.55%.

Ethyl 4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate, 2i

Recrystallized from EtOH. Yield: 82%; colourless solid; m.p. 182-84ºC; IR (KBr): 668, 757, 843, 854, 873, 956, 1018, 1068, 1093, 1112, 1127, 1170, 1216, 1288, 1326, 1367, 1392, 1425, 1462, 1619, 1646, 1703, 2401, 2982, 3020, 3116, 3243 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.09 (t, J = 7.44 Hz, 3H), 2.25 (s, 3H), 3.98 (q, J = 7.00 Hz, 2H), 5.28 (d, J = 2.80 Hz, 1H), 7.36 – 7.41 (d, J = 8.21, 2H) 7.45 – 7.50 (d, J = 8.21, 2H), 9.07 (brs, 1H); ^{13}C NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 13.09, 17.21, 53.35, 58.56, 98.30, 124.19, 126.07, 147.61, 151.91, 164.54. Anal. Calcd for $C_{15}H_{14}F_3NO_4$: C, 54.71; H, 4.29; N, 4.25. Found: C, 54.63; H, 4.21; N, 4.20%.

Methyl 2-(ethoxycarbonyl)-3-oxo-1-phenylbutyl-carbamate, 3

Recrystallized from EtOH. Yield: 90%; colourless solid; m.p. 69-71ºC; IR (KBr): 668, 699, 720, 928, 1029, 1044, 1215, 1359, 1456, 1509, 1719, 2400, 2856, 2927, 3020, 3424 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.10 – 1.22 (m, 3H), 2.15 – 2.32 (d, J = 6.74 Hz, 3H), 3.65 – 3.67 (d, J = 5.24 Hz, 3H), 4.02 – 4.20 (m, 2H), 5.47 (m, 1H), 6.07 – 6.39 (m, 1H), 7.30 (m, 5H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 13.61, 28.78, 30.00, 52.00, 54.32, 61.53, 63.36, 64.03, 126.08, 126.44, 127.54, 128.43, 139.23, 139.38, 156.14, 156.26, 166.88, 168.28, 200.36, 202.62. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.40; H, 6.51; N, 4.89%.

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References

1 Corey E J & Cheng X M, *The Logic of Chemical Synthesis* (John Wiley & Sons, New York), **1989**, 423.

2 (a) Kobayashi M, Kitazawa M, Saito T, Yamamoto R, Harada H & Yakugaku Z, 104, **1984**, 659; *Cicero Abstr*, 102, **1985**, 6344m.
(b) Engel J, Emig P, Nickel B & Szelenyi I, *Ger Often DE* 3.915.184; *Chem Abstr,* 112, **1990**, 2352861.
(c) Rajadhyaksha V J, *PCT Int Appl WO* 90,00407; *Chem Abstr*, 113, **1990**, 59177t.
(d) Testa E, Fontanella L, Cristiani G & Gallo G, *J Org Chem*, 24, **1959**, 1928.
(e) Franran C P, Douzon C, Raynaud G M & Serganl M Y, *US Pat* 3.821.215; *Chem Abstr*, 82, **1975**, 49951r.

3 Wang Y F, lzawa T, Kobayashi S & Ohno M, *J Am Chem Soc*, 104, **1982**, 6465.

4 Hirama M, Shigemoto T & Ito S, *J Org Chem*, 52, **1987**, 3342 and references cited therein.

5 (a) Schunk S & Enders D, *Org Lett*, 3, **2001**, 3177.
(b) Gregori J, Gonzalez-Rosende M E & Orena M, *Tetrahedron Asymmetry,* 11, **2000**, 3769.
(c) Lohray B B, Baskaran S, Reddy B Y & Rao K S, *Tetrahedron Lett*, 39, **1998**, 6555.
(d) Fujita M, Kitagawa O, Suzuki T & Taguchi T, *J Org Chem,* 62, **1997,** 7330.
(e) Dewynter G, Abdaoui M, Regainia Z & Montero J L, *Tetrahedron,* 52, **1996**, 14217.
(f) Walsh P J, Bennani Y L & Sharpless K B, *Tetrahedron Lett,* 34, **1993**, 5545.
(g) Baba A, Shibata I, Fujiwara M & Matsuda H, *Tetrahedron Lett,* 26, **1985**, 5167.
(h) Muhlstadt M & Kidera R, *Tetrahedron Lett,* 24, **1983**, 3979.

6 Paraskar A S, Dewkar G K & Sudalai A, *Tetrahedron Lett*, 44, **2003**, 3305.

7 Xu L W, Wang Z T, Xia C G & Zhao P Q, *Helv Chim Acta,* 87, **2004**, 2608.