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A $SiCl_4$–$ZnCl_2$ induced general, mild and efficient one-pot, three-component synthesis of β-amido ketone libraries

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Abstract—A general, mild and efficient protocol for the synthesis of β-amido ketone libraries was achieved utilizing tetrachlorosilane and zinc chloride in dichloromethane at ambient temperature via a one-pot, three-component condensation of various aldehydes, ketones and nitriles.

β-Amido ketones are important building blocks and intermediates in synthesis, for example, they are important precursors of heterocycles[1] as well as of β-amino alcohols, which are common units in both natural and synthetic biologically or pharmacologically important compounds.[2] Multicomponent coupling reactions[3] (MCRs) are attractive for parallel synthesis as large arrays of compounds with diverse substitution patterns can be prepared in one-step, often in high yields, under mild conditions. MCRs are powerful tools in modern drug discovery and allow fast, automated and high throughput synthesis of diverse structural scaffolds required in the search of novel therapeutic molecules. Recently, a number of reports have described the synthesis of β-acetamido ketones through multicomponent condensation of aryl aldehydes, enolizable ketones, acetyl chloride and acetonitrile catalyzed by $CoCl_2$,[4] Montmorillonite K-10 clay[5] or SiO_2–H_2SO_4[6] under thermal conditions or by using $ZrOCl_2{\cdot}8H_2O$[7] or $BiCl_3$ generated in situ from BiOCl and acetyl chloride[8] at room temperature. Although, these protocols are valuable, they lack the generality to produce arrays of β-amido ketones as they are restricted to acetonitrile giving the corresponding β-acetamido ketones,[4–8] and only one example of a β-benzamido ketone was prepared by this method involving benzonitrile in a long time (36 h).[7] To our knowledge, except for acetonitrile or benzonitrile, no other nitriles have been used in such condensations. Therefore, the introduction of new and efficient methods for this multicomponent reaction are still required. Towards this goal, and in continuation of our investigations[9] on the development and applications of new in situ reagents derived from tetrachlorosilane (TCS)[10] in organic synthesis, we have developed an efficient, general and convenient protocol for the one-pot synthesis of β-amido ketones. The reaction proceeds via a three-component reaction of various aldehydes, ketones and nitriles including alkyl, aralkyl, aryl and α,β-unsaturated nitriles as well as cyano esters utilizing the inexpensive and readily available tetrachlorosilane–zinc chloride reagent[10e] in dichloromethane at room temperature without using acetyl chloride.

An equimolar mixture of benzaldehyde, acetophenone and acetonitrile in dichloromethane was allowed to react in the presence of TCS (4 equiv) and $ZnCl_2$ (2 equiv) at room temperature to furnish the corresponding β-acetamido ketone **4a** in good yield (Table 1, entry 1). In order to create a library of compounds, we have reacted various ketones, aldehydes, and nitriles to afford a diverse set of β-amido ketones (Scheme 1, Table 1).

As seen from the results in Table 1 and Scheme 2, the reaction proved to be general and tolerated a variety of functional groups on the aromatic aldehydes, including chlorine, methyl and methoxy as well as sterically hindered aldehydes such as naphthaldehyde (Table 1, entries 2–4 and 7). A unique example of heteroaryl as well as α,β-unsaturated aldehydes was introduced through the MCR of 3-formylchromone with acetophenone and

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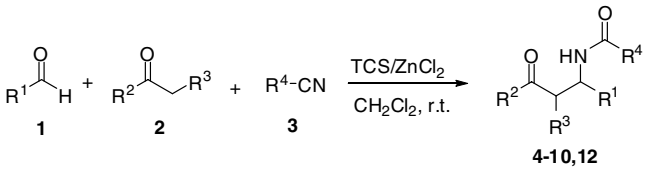
Table 1. $SiCl_4$–$ZnCl_2$ induced one-pot, three-component reaction of aldehydes with ketones and nitriles giving the corresponding β-amido ketones

Entry	R^1	R^2	R^3	R^4	Product	Time (h)	Yield[a] (%)
1	Ph	Ph	H	Me	**4a**	8	71
2	4-ClC_6H_4	Ph	H	Me	**4b**	9	69
3	4-MeC_6H_4	Ph	H	Me	**4c**	10	72
4	4-$MeOC_6H_4$	Ph	H	Me	**4d**	9	74
5	4-MeC_6H_4	4-MeC_6H_4	H	Me	**4e**	8	70
6	4-$MeOC_6H_4$	4-MeC_6H_4	H	Me	**4f**	11	73
7	2-Naphthyl	Ph	H	Me	**4g**	10	66
8	2-Chromonyl	Ph	H	Me	**5**	13	62
9	4-MeC_6H_4	Ph	H	$PhCH_2$	**6a**	11	65
10	4-$MeOC_6H_4$	Ph	H	$PhCH_2$	**6b**	10	68
11	4-MeC_6H_4	4-MeC_6H_4	H	$PhCH_2$	**6c**	13	66
12	4-$MeOC_6H_4$	4-MeC_6H_4	H	$PhCH_2$	**6d**	12	67
13	4-ClC_6H_4	Ph	H	Ph	**7a**	20	60
14	4-MeC_6H_4	Ph	H	Ph	**7b**	18	61
15	4-$MeOC_6H_4$	Ph	H	Ph	**7c**	17	63
16	Ph	4-MeC_6H_4	H	Ph	**7d**	18	61
17	4-$MeOC_6H_4$	4-MeC_6H_4	H	Ph	**7e**	16	62
18	4-MeC_6H_4	Ph	H	CH_2=CH–	**8a**	12	66
19	4-$MeOC_6H_4$	Ph	H	CH_2=CH–	**8b**	11	64
20	Ph	4-MeC_6H_4	H	CH_2=CH–	**8c**	11	67
21	4-MeC_6H_4	4-MeC_6H_4	H	CH_2=CH–	**8d**	12	65
22	4-$MeOC_6H_4$	4-MeC_6H_4	H	CH_2=CH–	**8e**	10	68
23	4-MeC_6H_4	Ph	H	CH_2COOEt	**9a**	11	70
24	4-$MeOC_6H_4$	Ph	H	CH_2COOEt	**9b**	10	72
25	4-MeC_6H_4	4-MeC_6H_4	H	CH_2COOEt	**9c**	11	71
26	4-$MeOC_6H_4$	4-MeC_6H_4	H	CH_2COOEt	**9d**	10	69
27	4-MeC_6H_4	1-Tetralone		Me	**10**	12	65
28	2-Naphthyl	1-Tetralone		—	**11**	18	87
29	4-$MeOC_6H_4$	1-Benzosuberone		Me	**12**	13	67

[a] Isolated yields after column chromatography except for product **11**, purified by recrystallization from EtOH.

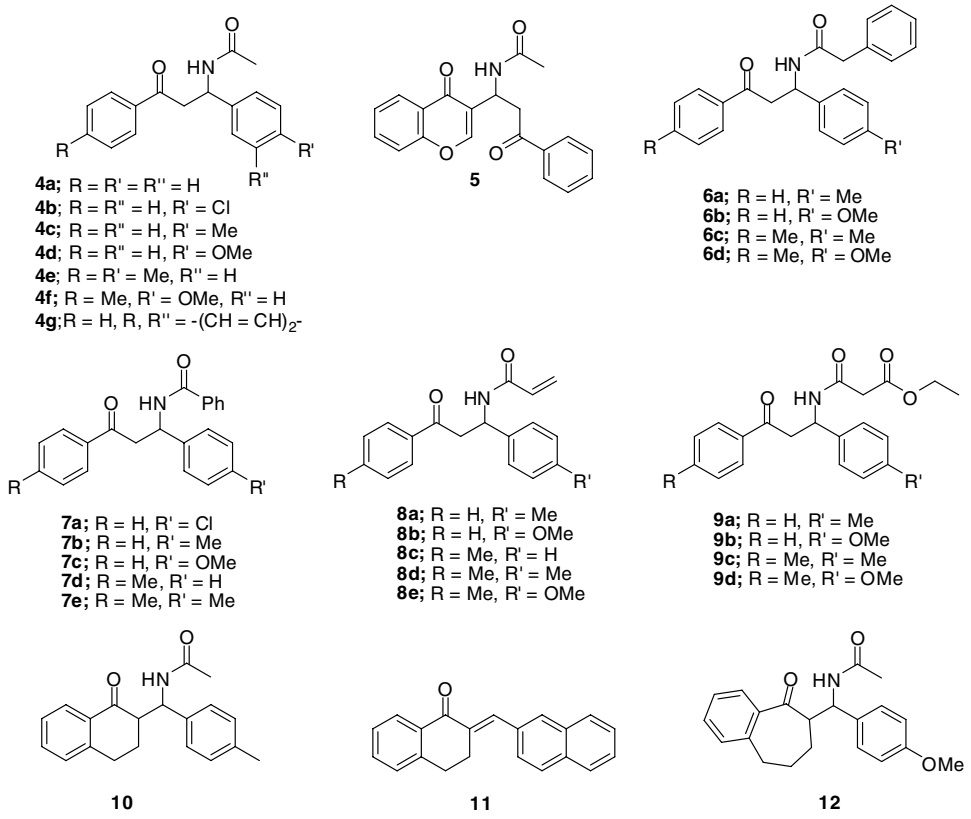


Scheme 1.

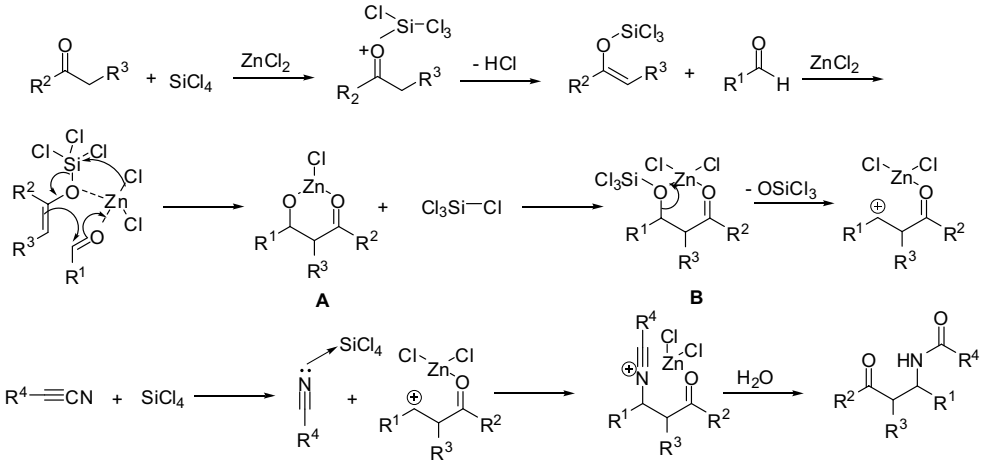
acetonitrile, which gave β-acetamido ketone **5** in moderate yield (Table 1, entry 8). It is appeared that the reaction with α-substituted enolisable ketones (entries 27 and 29) proceeds in a diastereoselective manner, however, we could not state which diastereoisomer is preferred at moment. Further investigations on the diastereoselectivity of the process are currently in progress in our lab. With respect to the ketones, the present reaction tolerated aryl methyl ketones as well as carbocyclic ketones such as 1-tetralone and 1-benzosuberone (Table 1, entries 27 and 29) giving the respective β-amido ketones in moderate yields. As with aldehydes, the present procedure works well with sterically hindered ketones (Table 1, entries 27 and 29). However, using two sterically hindered components in this reaction gave only the corresponding enone. Thus, the MCR of 1-tetralone with 2-naphthaldehyde and acetonitrile gave exclusively 2-naphthylidene-1-tetralone **11** even when using an excess of TCS and $ZnCl_2$ for a longer reaction time (up to 8 equiv, Table 1, entry 28). The reaction was successful with a variety of nitriles. Thus, besides acetonitrile, the MCRs of aldehydes and ketones with aralkyl, aryl and α,β-unsaturated nitriles as well as with cyanoesters were studied. Phenylacetonitrile, benzonitrile, acrylonitrile and ethyl cyanoacetate were chosen as representative examples. In all the cases studied, the reaction proceeded smoothly under the above conditions giving the corresponding β-amido ketones, typically within 12 h, except for the reaction with benzonitrile where reaction times of up to 20 h were required, which might be attributed to steric factors as well as to the low nucleophilicity of benzonitrile (Table 1, entries 13–17).

To optimize the reaction conditions, we examined the reaction in various solvents. CH_2Cl_2 was found to be the most effective solvent while donor solvents such as diethyl ether completely inhibited the reaction. $SnCl_2$ as a Lewis acid was examined and similar results were obtained but it was less effective than $ZnCl_2$. It is noteworthy to mention that no reaction was observed in the absence of either the Lewis acid or $SiCl_4$.

A reasonable mechanism for the present reaction may proceed as depicted in Scheme 3 in an aldol-type[11] way followed by amidoalkylation.[12] The addition of nucleophiles to the ketones is promoted by co-ordination of a Lewis acid to the carbonyl group enhancing the electrophilicity of this moiety.[13] On the other hand, use of $ZnCl_2$ as a radical initiator as well as a chelating agent has been documented.[14] Therefore, a reaction pathway that involves activation of the ketones by $SiCl_4$



Scheme 2.



Scheme 3.

is reasonable in analogy to the Me_3SiX assisted addition.[15] We presume that the mechanism is formally analogous to the Lewis acid-catalyzed addition of silyl enol ethers to carbonyl compounds. Indeed, the reaction may proceed via the prior complexation of the –CO– with $ZnCl_2$ according to the well established Zimmerman–Traxler chair-like transition state model[16] to afford the corresponding silyl zinc chelate **A**,[17] which is converted to silyl zinc chelate **B**. On the other hand, as with $SnCl_4$[18a] $SiCl_4$ may co-ordinate with nitriles activating addition of the nitrile to the silyl zinc chelate **B** in a manner similar to the Ritter reaction[19] giving eventually the desired β-amido ketone after aqueous work-up.

According to the proposed mechanism, the reaction may be viewed as a new route to β-amido ketones via a mild tandem aldol-amidoalkylation reaction sequence. It is noteworthy to mention that only a few examples of β-amido ketones of type **6** and **7** have previously been prepared via multi-step routes under harsh conditions.[18]

In conclusion, we have reported $SiCl_4$–$ZnCl_2$ as a readily available and inexpensive reagent for the efficient

one-pot, three-component synthesis of β-amido ketone libraries through a tandem aldol-amidoalkylation reaction under very mild conditions.[20] The present protocol is convenient and applicable to a wide variety of aldehydes, ketones and nitriles, which should make it amenable to high throughput synthesis of combinatorial libraries for potential drug development.

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20. A typical procedure for the MCR of **1**, **2** and **3** with $SiCl_4$/$ZnCl_2$: To a solution of anhydrous $ZnCl_2$ (1.35 g, 10 mmol) in CH_2Cl_2 (20 ml) were added aldehyde (5 mmol), ketone (5 mmol) and nitrile (5 mmol). The reaction mixture was stirred at ambient temperature for 10 min, $SiCl_4$ (2.4 ml, 20 mmol) was added and the reaction mixture was stirred with exclusion of moisture. On completion (TLC monitoring of the progress of the reaction), the mixture was poured onto water (100 ml), extracted with CH_2Cl_2 (2×50 ml) and the combined organic extract dried over anhydrous $MgSO_4$, evaporated and the residue chromatographed on silica gel using pet. ether–ethyl acetate (2:1) as eluent to give pure β-amido ketones. Spectral data for representative examples of β-amido ketones are listed below.
N-(3-Chromonyl-3-oxo-3-phenylpropyl)-acetamide **5**: mp 188–190 °C. $R_f = 0.22$, (pet. ether/AcOEt 1:1); IR (KBr) ν 3311, 3078, 2920, 1679, 1643, 1575, 1545, 1465, 1402, 1359, 1319, 1282, 1222, 1161, 1143, 990, 810, 759, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 8.13 (d, $J = 8.2$ Hz, 1H), 7.88 (d, $J = 7.9$ Hz, 2H), 7.64 (t, $J = 7.6$ Hz, 1H), 7.41–7.50 (m, 4H), 7.39 (s, 1H), 7.21 (t, $J = 6.9$ Hz, 1H, NH exchanged with D_2O), 5.52 (q, $J = 4.45$ Hz, 1H), 3.80 (dd, $J = 3.97$, 17.5 Hz, 1H), 3.50 (dd, $J = 3.97$, 17.6 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.29, 180.13, 169.39, 155.87, 149.23, 136.48, 133.29, 132.19, 129.17, 128.53, 127.09, 124.43, 123.62, 114.54, 113.21, 49.62, 43.31, 23.23; Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.76; H, 5.07; N, 4.22.

N-[1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl]-2-phenylacetamide **6b**: mp 131–132 °C. $R_f = 0.18$, (pet. ether/AcOEt 2:1); IR (KBr) ν 3275 (NH), 3064, 3030, 2926, 1686 (CO), 1646 (CONH), 1613, 1550, 1513, 1450, 1358, 1249, 1200, 1177, 1030, 993, 757, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, $J = 7.8$ Hz, 2H), 7.52 (t, $J = 7.2$ Hz, 1H), 7.42–7.2 (m, 7H), 7.18 (d, $J = 8.7$ Hz, 2H), 6.74 (m, 3H), 5.48 (q, $J = 6.3$ Hz, 1H), 3.7 (s, 3H), 3.62 (dd, $J = 5.5$, 16.6 Hz, 1H), 3.52 (s, 2H), 3.29 (dd, $J = 5.5$, 16.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.1, 170.21, 158.61, 136.49. 134.76, 133.24, 132.82, 129.18, 128.76, 128.51, 127.98, 127.48, 127.08, 113.8,55.06, 49.51, 43.62, 43.3; MS (*m*/*z*, %): 373 (M^+, 40.8), 374 (M^++1, 14), 254 (100), 223 (53), 19 (100); Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.12; H, 6.17; N, 3.51.

N-[1-(4-Methylphenyl)-3-oxo-3-phenylpropyl]-benzamide **7b**: mp 172–173 °C. $R_f = 0.4$, (pet. ether/AcOEt 2:1); IR (KBr) ν 3279 (NH), 3071, 2955, 1683 (CO), 1642 (CONH), 1599, 1578, 1446, 1405, 1359, 1303, 1198, 1264, 1226, 1157, 1083, 983, 800, 761, 650, 600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, $J = 7.8$ Hz, 2H), 7.80 (d, $J = 7.8$ Hz, 2H), 7.58 (d, $J = 5.3$, 1H, NH), 7.47 (m, 6H), 7.31 (m, 2H), 7.10 (d, $J = 7.8$ Hz, 2H), 5.73 (q, $J = 5.1$ Hz, 1H), 3.86 (dd, $J = 5.5$, 16.95 Hz, 1H), 3.51 (dd, $J = 5.5$, 16.95 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.00, 170.24, 137.73, 136.91, 136.35, 134.76, 133.28, 129.23, 129.17, 128.81, 128.54, 128.01, 127.14, 126.18, 49.73, 43.25, 20.92; Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.22; H, 6.02; N, 3.79.

N-[1-(4-Methylphenyl)-3-oxo-3-(4-methylphenyl)propyl]-acrylamide **8d**: mp 102–103 °C. $R_f = 0.51$, (pet. ether/AcOEt 1:1); IR (KBr) ν 3264 (NH), 3059, 2920, 1680 (CO), 1651 (CONH), 1411, 1360, 1268, 1181, 992, 810, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, $J = 8$ Hz, 2H), 7.24 (d, $J = 10$ Hz, 4H), 7.11 (d, $J = 8$ Hz, 2H), 6.82 (d, $J = 6$ Hz, 1H), 6.31 (dd, $J = 5.4$, 16.5 Hz, 1H), 6.11 (m, 1H), 5.61 (m, 2H), 3.77 (dd, $J = 6$, 16 Hz, 1H), 3.42 (dd, $J = 6$, 16 Hz, 1H), 2.42 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.61, 164.13, 144.32, 139.81, 134.13, 133.07, 131.19, 128.20, 128.03, 127.94, 126.87, 126.32, 49.52, 43.08, 21.61, 21.39; Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.02; H, 7.03; N, 4.33.

N-[1-(4-Methylphenyl)-3-oxo-3-(4-methylphenyl)propyl]-2-carbethoxyacetamide **9c**: mp 104–106 °C. $R_f = 0.41$, (pet. ether/AcOEt 2:1); IR (KBr) ν 3283 (NH), 3092, 2980, 1745 (COOEt), 1683 (CO), 1650 (CONH), 1608, 1564, 1515, 1409, 1361, 1234, 1151, 1034, 811 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.1 (d, $J = 6$ Hz, 1H), 7.87 (d, $J = 7.8$ Hz, 2H), 7.30(d, $J = 7.6$ Hz, 4H), 7.17 (d, $J = 7.4$ Hz, 2H), 5.62 (q, $J = 6.4$ Hz, 1H), 4.25 (q, $J = 7$ Hz, 2H), 3.75 (dd, $J = 5.2$, 16.4 Hz, 1H), 3.46 (m, 1H), 3.39 (s, 2H), 2.47 (s, 3H), 2.37 (s, 3H), 1.36 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.81, 171.52, 168.10, 141.07, 139.18, 135.17, 133.54, 128.27, 128.13, 128.00, 126.12, 49.36, 43.72, 42.25, 56.31, 21.41, 21.23, 19.42; MS (*m*/*z*, %): 367 (M^+, 27), 368 (M^++1, 8), 322 (4), 276 (7), 253 (19), 252 (100), 236 (12), 221 (18), 134 (39), 119 (87); Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.68; H, 6.77; N, 3.87.

2-[N-Acetylamino(4-methoxyphenyl)methyl]-1-benzosuberone **12**: mp 166 °C. $R_f = 0.3$, (pet. ether/AcOEt 1:1); IR (KBr) ν 3356, 2997, 2933, 2860, 1675, 1606, 1514, 1449, 1371, 1299, 1276, 1244, 1185, 1115, 1031, 980, 843, 582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, $J = 9.3$ Hz, 1H), 7.48 (d, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 7.5$ Hz, 1H), 7.19 (m, 4H), 6.77 (d, $J = 8.4$ Hz, 2H), 5.31 (dd, $J = 3.9$, 9.3 Hz, 1H), 3.50 (m, 1H), 3.76 (s, 3H), 3.00 (m, 2H), 2.20 (m, 1H), 2.06 (s, 3H), 1.90 (m, 2H), 1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.18, 169.65, 158.36, 142.68, 139.65, 133.31, 131.41, 130.11, 127.83, 127.64, 126.33, 113.61, 55.07, 53.77, 53.58, 33.83, 29.07, 25.30, 23.44; Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.38; H, 7.10; N, 4.09.