Tetrahedron Letters 52 (2011) 6103–6107

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted efficient one-step synthesis of amides from ketones and benzoxazoles from (2-hydroxyaryl) ketones with acetohydroxamic acid using sulfuric acid as the catalyst

Madabhushi Sridhar *, Chinthala Narsaiah, Vangipuram Venkata Sairam, Godala Kondal Reddy, Jillella Raveendra, Mallu Kishore Kumar Reddy, Beeram China Ramanaiah

Fluoroorganics Division, Indian Institute of Chemical Technology, Hyderabad 500 607, India

ARTICLE INFO

Article history:
Received 18 July 2011
Revised 29 August 2011
Accepted 4 September 2011
Available online 10 September 2011

Keywords:
Acetohydroxamic acid
Amides
Benzoxazoles
Microwave heating
Acid catalysis

ABSTRACT

Efficient one-step method for the synthesis of amides directly from ketones and benzoxazoles from (2-hydroxyaryl) ketones by the reaction of acetohydroxamic acid using sulfuric acid as catalyst was described.

© 2011 Elsevier Ltd. All rights reserved.

Amide functionality is ubiquitous in natural products and its formation is a fundamental reaction in organic synthesis.[1] Though a variety of methods for the preparation of amides are available in the literature,[2] the Beckmann rearrangement of a ketoxime into an amide stands as a powerful method for the preparation of amides, particularly for the manufacture of ε-caprolactam in the chemical industry.[3]

Preparation of amides from ketones is generally carried out in two steps. In the first step, ketone is converted into an oxime by the reaction with hydroxylamine hydrochloride in the presence of stoichiometric quantity of a base. In the second step, oxime is subjected to the Beckmann rearrangement using a Lewis or Bronsted acid as a catalyst to obtain amide. In the literature, however, methods for the direct conversion of ketone into amide in a single step are scarce and the only method known so far is by solvent-free heating of the mixture of a ketone, hydroxylamine hydrochloride (4.3 equiv), and ZnO (2.0 equiv) at >140 °C for 1–9 h.[4]

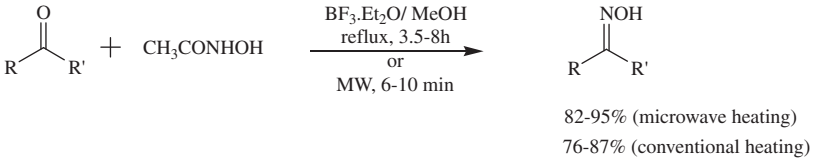
Acetohydroxamic acid (AHA) or $CH_3CONHOH$ or Lithostat® is a commercially available stable solid compound, which has important applications as a drug for the treatment of urinary tract infections[5] and as a chelating agent in UREX process for the recovery of uranium from spent nuclear fuel.[6] However, in organic chemistry, AHA has received little attention for the study of its synthetic applications and recently, we reported a novel application of AHA for the efficient conversion of carbonyls into oximes using $BF_3{\cdot}Et_2O$ as the catalyst under reflux in methanol as shown in Scheme 1.[7]

Oximes are known to undergo efficient conversion into amides through Beckmann rearrangement under Lewis or Bronsted acid catalysis.[8] However, in our previous study (Scheme 1), amides were not formed even in trace quantities with $BF_3{\cdot}Et_2O$ or with other Lewis and Bronsted acids as catalysts and only oxime or a mixture of oxime and oxime acetate under the reaction conditions was obtained. At this stage, we envisioned achieving direct conversion of ketones into amides exploring suitable conditions for the reaction. Our efforts in this direction gave us fruitful results and herein we report for the first time an efficient method for the preparation of amides directly from ketones with AHA using sulfuric acid as the catalyst under reflux in acetonitrile as shown in Scheme 2.

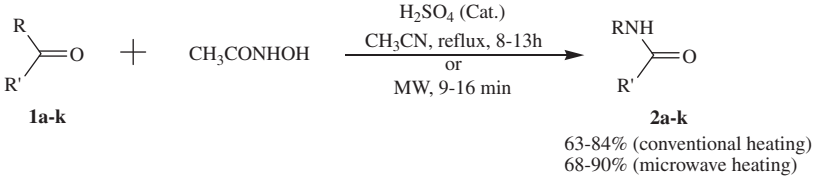
In our preliminary experiments, we studied the reaction of AHA and acetophenone using different combinations of acids and solvents to observe the formation of acetanilide. We screened the reaction with several Lewis and Bronsted acid catalysts, such as I_2, $ZnCl_2$, $InCl_3$, $BF_3{\cdot}Et_2O$, $Bi(OTf)_3$, $Eu(OTf)_3$, sulfuric acid, *p*-toluene sulfonic acid, acetic acid, hydrochloric acid, and trifluoroacetic acid using a variety of solvents, such as acetonitrile, toluene, tetrahydrofuran, dichloromethane, and methanol. In this study, we found the formation of acetanilide from acetophenone only with Bronsted

* Corresponding author. Tel.: +91 040 27191772; fax: +91 040 27160387.
E-mail address: smiict@gmail.com (S. Madabhushi).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.09.019

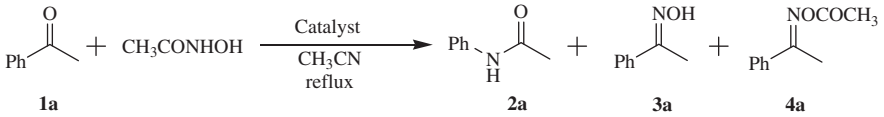


Scheme 1. Synthesis of oximes from carbonyls using acetohydroxamic acid.



Scheme 2. Synthesis of amides from ketones using acetohydroxamic acid.

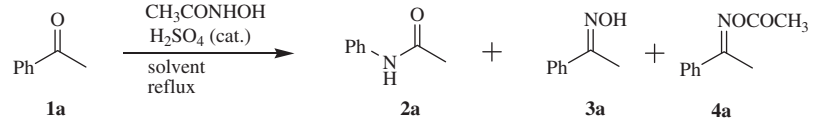
Table 1
Acid catalyzed conversion of acetophenone into acetanilide and acetophenone oxime



Entry	Catalyst[a]	Reaction Time (h)	% Yield[b]		
			2a	**3a**	**4a**
1	H_2SO_4	8.5	80	9	0
2	PTSA	24	35	64	0
3	CH_3COOH	24	0	67	0
4	HCl	24	0	50	0
5	CF_3COOH	24	30	65	0
6	I_2	10	0	53	0
7	$ZnCl_2$	12	0	62	0
8	$InCl_3$	15	0	68	0
9	$BF_3.Et_2O$	8	0	75	0
10	$Bi(OTf)_3$	13	0	72	0
11	$Eu(OTf)_3$	9	0	65	0

[a] 40 mol %.
[b] Isolated yields.

Table 2
Solvent effect on the reaction of acetophenone with acetohydroxamic acid.



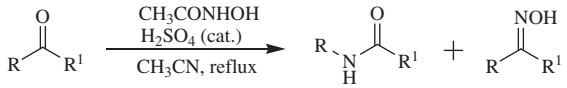
Entry	Solvent	Reaction Time (h)	% Yield[a]		
			2a	**3a**	**4a**
1	Acetonitrile	8.5	80	9	0
2	Toluene	12	0	62	0
3	Tetrahydrofuran	10	0	67	0
4	Dichloromethane	8	0	58	17
5	MeOH	6	0	86	0

[a] Isolated yields.

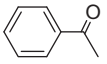
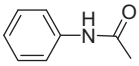
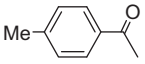
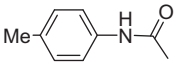
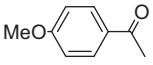
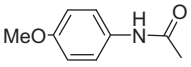
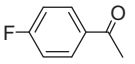
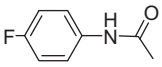
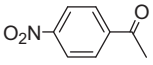
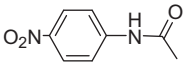
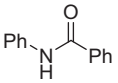
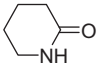
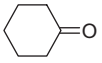
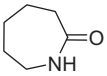
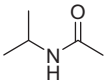
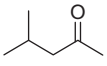
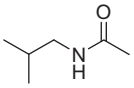
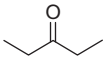
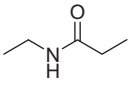
acids, such as sulfuric acid, trifluoroacetic acid, and *p*-toluene sulfonic acid under reflux in acetonitrile as shown in Table 1.

Sulfuric acid catalyzed the formation of acetanilide **2a** from acetophenone in 80% yield when the reaction was carried out under reflux in acetonitrile. In solvents, such as tetrahydrofuran, dichloromethane, and methanol, a mixture of acetophenone oxime **3a** and acetophenone oxime acetate **4a** were obtained as shown in Table 2.

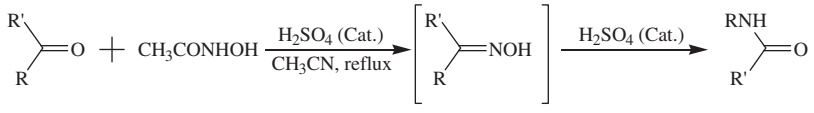
Table 3
Synthesis of amides from the reaction of ketones with acetohydroxamic acid



1a-k **2a-k** **3a-k**

Entry	Ketones, **1**	Amides, **2**	Microwave heating			Conventional heating		
			Time (min)	% Yield[a]		Time (h)	% Yield[a]	
				2	**3**		**2**	**3**
a			10	86	5	8.5	80	7
b			13	83	7	9.5	76	11
c			12	90	0	8	83	7
d			10	78	6	12	71	12
e			15	67	10	16	62	17
f			11	72	8	9.5	65	13
g			8	87	0	8	75	6
h			10	83	4	10.5	70	9
i			8	76	0	9.5	67	10
j			10	87	0	11.5	74	8
k			12	79	0	10.5	73	10

[a] Isolated yields. All products gave satisfactory ^{1}H and ^{13}C NMR, IR, and mass spectral data.



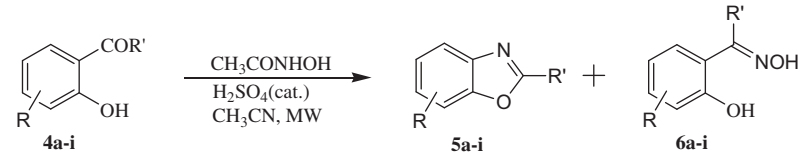
Scheme 3. Possible mechanism for the formation of amide.

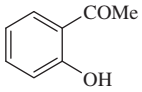
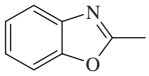
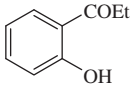
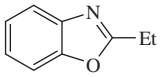
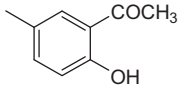
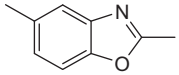
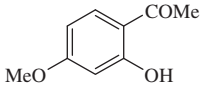
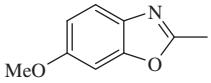
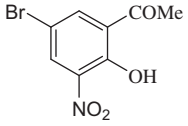
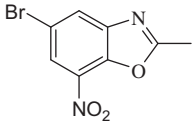
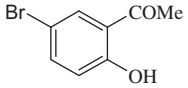
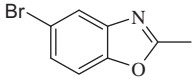
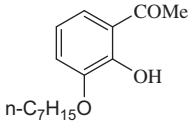
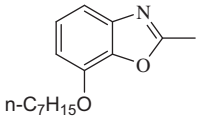
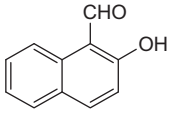
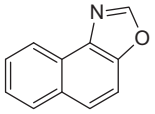
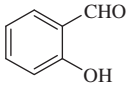
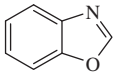
Next, we reacted AHA with a variety of ketones (e.g., aryl alkyl ketones, diarylketones, dialkyl ketones, and cyclic ketones) **1a–m** to obtain the corresponding amides **2a–m** in 63–83% and oximes **3a–m** in 0–10% yields using sulfuric acid as a catalyst under reflux in acetonitrile for 8–16 h. We have also studied these reactions under microwave heating conditions using sulfuric acid as a catalyst in acetonitrile and obtained amides **2a–m** in 68–90% yields and oximes **3a–m** in 0–17% yields in 8–15 min. Here, microwave heating was found to be more advantageous than conventional heating as it reduced the reaction time from several hours to few minutes. The representative results obtained in this study[9] are shown in Table 3.

In the above study, though we observed conversion of ketone into amide in one-step, we consider that this reaction proceeds through the formation of ketoxime as an intermediate, which could undergo rapid Beckmann rearrangement to amide under the reaction conditions as shown in Scheme 3. In our study, when acetophenone oxime was subjected to Beckmann rearrangement using sulfuric acid as a catalyst under reflux in acetonitrile, we obtained acetanilide in 98% yield in 30 min.

When (2-hydroxyaryl) ketones **4a–g** were reacted with AHA using sulfuric acid as a catalyst under microwave heating, we obtained benzoxazoles **5a–g** in good yields (53–83%). However, under similar conditions, (2-hydroxyaryl) aldehydes **4h** and **4i** gave the

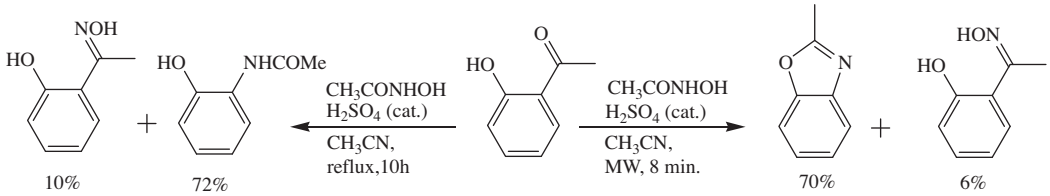
Table 4
One-step synthesis of benzoxazoles from (2-hydroxyaryl) ketones



Entry	(2-hydroxyaryl) ketone or aldehyde, **4**	benzoxazole,**5**	Microwave heating		
			Time (min)	% Yield[a]	
				5	**6**
a			8	70	6
b			10	76	0
c			8	68	10
d			12	72	8
e			8	83	0
f			10	65	7
g			0	78	0
h			12	32	15
i			8	28	12

[a] Isolated yields. All products gave satisfactory ^{1}H and ^{13}C NMR, IR, and mass spectral data.

corresponding benzoxazoles **5h** and **5i** in 32% and 28% yields, respectively, as shown in Table 4. In this study, **5h** and **5i** were obtained in low yields because aldehydes **4h** and **4i** showed less thermal stability under the reaction conditions and partly decomposed into a black mass. Benzoxazole is a privileged structural unit in a wide range of biologically active and medicinally important compounds[10] and benzoxazoles are generally prepared by treating (2-hydroxyaryl) ketone oxime with an acid catalyst.[11] The present



Scheme 4. Reaction of (2-hydroxy) acetophenone with acetohydroxamic acid.

work is the first method for the direct conversion of a (2-hydroxyaryl) ketone directly into benzoxazole.[12]

In our study, (2-hydroxyaryl) ketones were converted into benzoxazoles only under microwave heating. They gave mixtures of the corresponding amide and oxime under reflux in acetonitrile and the results obtained with (2-hydroxy) acetophenone under these conditions are shown as a typical example in Scheme 4.

In summary, this work shows an unprecedented efficient one-step method for the synthesis of amides from ketones and benzoxazoles from the reaction of (2-hydroxyaryl) ketones with acetohydroxamic acid using sulfuric acid as a catalyst in acetonitrile. In this study, amides were formed in good yields both under conventional and microwave heating conditions and we obtained benzoxazoles only with microwave heating. In both methods, the reaction times were found to be very short (<15 min) under microwave heating conditions.

Acknowledgments

C.N. is thankful to the UGC, New Delhi; J.R., G.K.R., and M.K.K.R are thankful to the CSIR, New Delhi for the award of Junior Research Fellowships. B.C.R. is thankful to the CSIR, New Delhi for the award of Senior Research Fellowship.V. V.S. is thankful to the Director, IICT for financial support in the form of fellowship.

References and notes

1. (a) Patai, S. *Chemistry of Carbon–Nitrogen Double Bond*; Wiley: London, 1970. pp 409–439; (b) Atta-ur-Rahman *Studies in Natural products*; Elsevier Science, 2000. p 24; (c) Wasserman, H. H. *Nature* **2006**, *441*, 699–700.
2. (a) Arisawa, M.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 311–312; (b) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2002**, *67*, 6272–6274; (c) Boruah, M.; Konwar, D. *J. Org. Chem.* **2002**, *67*, 7138–7139; (d) Iranpoor, N.; Firouzabadi, H.; Aghapour, G. *Synth. Commun.* **2002**, *32*, 2535–2541; (e) Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* **2003**, *44*, 755–756.
3. Ritz, J.; Fuchs, H.; Kieczka, H.; Moran, W. C. In *Caprolactam. Ullmann's Encyclopedia of Industrial Chemistry*; Cambell, F. Th., Pfefferkorn, R., Rounsaville, J. R., Eds.; Wiley-VCH: Weinheim, 1986; Vol. 5, pp 31–50.
4. Sharghi, H.; Hosseini, M. *Synthesis* **2002**, 1057–1060.
5. Griffith, D. P.; Gleeson, M. J.; Lee, H.; Longuet, R.; Deman, E.; Earle, N. *Eur. Urol.* **1991**, *20*, 243–247.
6. Tkac, P.; Matteson, B.; Bruso, J.; Paulenova, A. *J. Radioanal. Nucl. Chem.* **2008**, *277*, 31–36.
7. Sridhar, M.; Narsaiah, C.; Raveendra, J.; Reddy, G. K.; Reddy, M. K. K.; Ramanaiah, B. C. *Tetrahedron Lett.* **2011**, *52*, 4701–4704.
8. (a) Beckmann, E. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 988–993; (b) Donaruma, L. G.; Heldt, W. Z. *Org. React.* **1960**, *11*, 1–156; (c) Gawley, R. E. *Org. React.* **1988**, *35*, 1–420.
9. *Typical procedure for the preparation of amide under conventional heating:* Acetophenone **1a** (1.0 g, 8.3 mmol), acetohydroxamic acid (0.92 g, 12.5 mmol), acetonitrile (10 ml), and conc. H_2SO_4 (0.2 ml) were taken into a 25 ml round bottomed flask fitted with a condenser and calcium chloride guard tube. The mixture was refluxed and the progress of the reaction was monitored by tlc. After completion of the reaction (8.5 h), the reaction mixture was cooled to room temperature and diluted with ethyl acetate (5 ml). Next, saturated sodium bicarbonate solution (10 ml) was added drop-wise to the mixture for the neutralization of sulfuric acid and then extracted with ethyl acetate (2×10 ml). The combined organic layer was washed with saturated NaCl solution, dried over anhy. Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by normal column chromatography (silica gel 60–120 mesh, ethyl acetate/hexane: 1:4) to obtain acetanilide **2a** (0.89 g, 80%, mp 114–116 °C) and acetophenone oxime **3a** (76 mg, 7%, mp 55–60 °C) in the form of white powders.
Spectral data obtained for **2a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (bs, 1H, exchangeable with D_2O), 7.44–7.51 (d, J = 7.9 Hz, 2H), 7.23–7.31 (t, J = 7.9 Hz, 2H), 7.02–7.09 (t, J = 7.9 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2, 138.3, 129.2, 124.6, 120.4, 24.8; IR (neat): υ 3245, 3070, 2960, 2833, 1654, 1607, 1511, 1369, 1243, 1027, 830, 770, 526 cm^{-1}; EIMS (m/z, %): 135 $(M)^+$, 93, 77. Exact mass observed for C_8H_9NO: 135.1635 (calcd: 135.1613).
Spectral data obtained for **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.42 (bs, 1H, exchangeable with D_2O), 7.54–7.62 (m, 2H), 7.32–7.41 (m, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 157.6, 130.5, 127.6, 118.4, 117.4, 14.5; IR (neat): υ 3380, 2924, 1620, 1574, 1494, 1292, 1257, 989, 643 cm^{-1}; EIMS (m/z, %): 135 $(M)^+$, 118, 103, 77, 51. Exact mass observed for C_8H_9NO: 135.0684 (calcd: 135.0632).
Typical procedure for the preparation of amide under microwave heating: Acetophenone **1a** (1.0 g, 8.3 mmol), acetohydroxamic acid (0.92 g, 12.5 mmol), acetonitrile (3 ml), and conc. H_2SO_4 (0.2 ml) were taken into a 10 ml pressure tube and subjected to microwave heating (CEM discover, 360 W, 80 °C, 25 psi) for 10 min. The crude product obtained was purified as mentioned above to afford acetanilide **2a** (0.94 g, 86%) and it gave spectral data same as above.
10. For some recent examples, see: (a) Oksuzoglu, E.; Tekiner-Gulbas, B.; Alper, S.; Temiz-Arpaci, O.; Ertan, T.; Yildiz, I.; Diril, N.; Sener-Aki, E.; Yalcin, I. *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 37–42; (b) McKee, M. L.; Kerwin, S. M. *Bioorg. Med. Chem.* **2008**, *16*, 1775; (c) Johnson, S. M.; Connelly, S.; Wilson, I. A.; Kelly, J. W. *J. Med. Chem.* **2008**, *51*, 260–270; (d) Harikrishnan, L. S.; Kamau, M. G.; Herpin, T. F.; Morton, G. C.; Liu, Y.; Cooper, C.; Salvati, M. E.; Qiao, J. X.; Wang, T. C.; Adam, L. P.; Taylor, D. S.; Chen, A. Y. A.; Yin, X.; Seethala, R.; Peterson, T. L.; Nirschl, D. S.; Miller, A. V.; Weigelt, C. A.; Appiah, K. K.; O'Connell, J. C.; Lawrence, R. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2640–2644; (e) Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272–4277; (f) Lokwani, P.; Nagori, B. P.; Batra, N.; Goyal, A.; Gupta, S.; Singh, N. *J. Chem. Pharm. Res.* **2011**, *3*, 302–311.
11. (a) Sardarian, A. R.; Shahsavari-Fard, Z. *Synlett* **2008**, 1391–1393; (b) Loupy, A.; Regnier, S. *Tetrahedron Lett.* **1999**, *40*, 6221–6224; (c) Haley, M. F.; Yates, K. *Can. J. Org.Chem.* **1987**, *52*, 1825–1830; (d) Stokker, G. *J. Org. Chem.* **1983**, *48*, 2613–2615.
12. *Typical procedure for the preparation of benzoxazoles under microwave heating:* 2-Hydroxy acetophenone **4a** (1.0 g, 7.4 mmol), acetohydroxamic acid (0.83 g, 11.0 mmol), acetonitrile (3 ml), and conc. H_2SO_4 (0.2 ml) were taken into a 10 ml pressure tube and subjected to microwave heating (CEM discover, 360 W, 80 °C, 25 psi) for 8 min. Next, the reaction mixture was diluted with ethyl acetate (3 ml) and to this; saturated sodium bicarbonate solution (5 ml) was added drop-wise. The mixture was extracted with ethyl acetate (2×10 ml) and the combined organic layer was washed with saturated NaCl solution, dried over anhy. Na_2SO_4, and concentrated under reduced pressure. Purification of the mixture by normal column chromatography (silica gel 60–120 mesh, ethyl acetate/hexane: 1:9) gave benzoxazole **5a** (0.67 g, 70%) in the form of a yellow oil and 2-hydroxy acetophenone oxime **6a** (68 mg, 6%, mp 104–107 °C) in the form of a white powder.
Spectral data obtained for **5a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.63 (m, 1H) 7.39–7.42 (m, 1H), 7.22–7.26 (m, 2H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6, 150.9, 141.3, 124.4, 124.1, 119.4, 110.1, 14.4; IR (neat): υ 2927, 2846, 1701, 1639, 1546, 1525, 1493, 1444, 1243, 1024, 816, 720 cm^{-1}; EIMS (m/z, %): 133 $(M)^+$,118, 92, 52. Exact mass observed for C_8H_7NO: 133.0528 (calcd: 135.0473).
Spectral data obtained for **6a**: ^{1}H NMR (300 MHz, CDC_{l3}): δ = 11.52 (bs, 1H, exchangeable with D_2O), 8.13 (bs, 1H, exchangeable with D_2O), 7.37–7.40 (d, J = 8.3 Hz, 1H), 7.19–7.25 (t, J = 8.3,6.7 Hz,1H), 6.91–6.95 (d, J = 6.7 Hz, 1H), 6.83–6.88 (t, J = 8.3, 6.7 Hz,1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 157.3, 130.8, 127.6, 119.4, 117.2, 10.8; IR (neat): υ 3380, 2924, 1620, 1574, 1494, 1292, 1257, 989, 643 cm^{-1}; EIMS (m/z, %): 151 (M^+), 134, 119, 93, 41. Exact mass observed for $C_8H_9NO_2$: 151.1525 (calcd: 151.1519).