HETEROCYCLES, Vol. 93, No. 2, 2016, pp. 816 - 823. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 28th September, 2015, Accepted, 30th November, 2015, Published online, 10th December, 2015
DOI: 10.3987/COM-15-S(T)59

$Yb(OTf)_3$-CATALYZED SYNTHESIS OF 2-SUBSTITUTED 4(3*H*)-QUINAZOLINONES VIA CLEAVAGE OF A CARBON-CARBON BOND

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Abstract — A general, selective, and practical one-pot synthesis of 2-substituted 4(3*H*)-quinazolinones by the $Yb(OTf)_3$-catalyzed *cyclo*-condensation of 2-aminobenzamides with acyclic or cyclic 1,3-diketones (*β*-diketones) under mild and neutral reaction conditions has been developed, which involves the highly selective cleavage of a C-C bond in 1,3-diketones by $Yb(OTf)_3$ catalyst. For example, the $Yb(OTf)_3$-catalyzed *cyclo*-condensation of 2-aminobenzamide (**1a**) with 1-phenylbutane-1,3-dione (**2c**) gave 2-methyl-4(3*H*)-quinazolinone (**3a**) in 90% yield, together with acetophenone in 65% yield. Ring-opening *cyclo*-condensation of 2-aminobenzamides (**1a**) with cyclic 1,3-diketones (**2i** and **2k**-**m**), except for cyclopentane-1,3-dione (**2j**), gave 2-substitued 4(3*H*)-quinazolinones (**3i** and **3k**-**m**) with one carbonyl group.

4(3*H*)-Quinazolinones belong to one of the most important classes of fused heterocyclic compounds and

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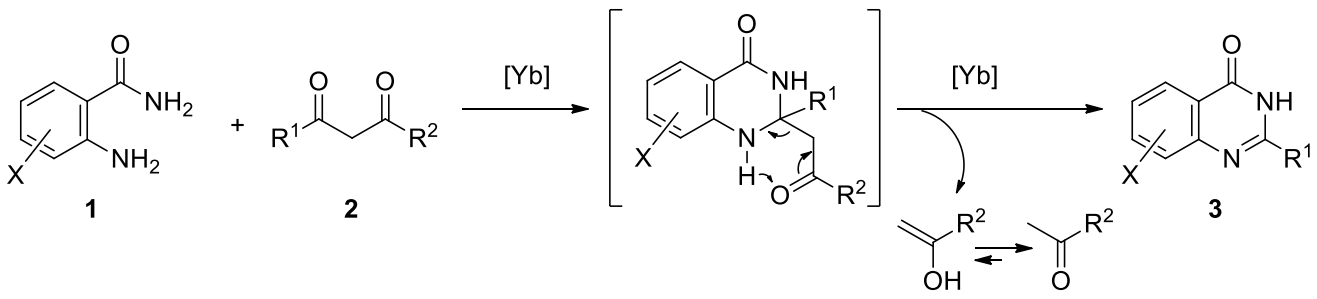
Dedicated with respect to Professor Dr. Lutz F. Tietze on the occasion of his 75th birthday

have a wide range of biological activities.[1] Various methods for the synthesis of 4(3*H*)-quinazolinones have been developed and reported,[2] almost all of which are based on the condensation of 2-aminobenzoic acid (anthranilic acid) with carbonyl compounds (aldehydes or ketones) and amines, i.e., the Niementowski synthesis.[3] However, these methods suffer from multi-step and tedious procedures, costly reagents, and often low yields. Three reactions that have attracted the interest of organic and organometallic chemists have been reported independently. Manhas reported the pioneering synthesis of 2-methyl-3-aryl-4(3*H*)-quinazolinones from the reaction of 2-amino-*N*-arylbenzamides and pentane-2,4-dione (acetylacetone) under acidic reaction conditions (6% ethanolic hydrogen chloride), involving *retro*-Aldol reaction of pentane-2,4-dione,[4] and Pihlaja reported a three-step synthesis of 2-methyl-4(3*H*)-quinazolinone from 2-aminobenzamide with 1-(4-substituted)phenylbutane-1,3-dione via *Z*-enamine intermediates which underwent cyclization followed by elimination of aryl methyl ketones under acidic reaction conditions (with trifluoroacetic acid for one week).[5] Wang developed an iodine-catalyzed ring-opening condensation of 5,5-dimethyl-1,3-cyclohexadienone (dimedone) with 2-aminobenzamides to give bis-quinazolin-4(3*H*)-ones.[6] Unfortunately, the applicable substrates were strictly limited in the above three reactions,[4-6] and the reactions were generally carried out under acidic reaction conditions[4,5] or in the presence of I_2.[6]

As a continuation of our study on the rare earth metal-catalyzed synthesis of heterocyclic compounds,[7] we succeeded in developing a general, selective, and practical one-pot synthesis of 2-substituted 4(3*H*)-quinazolinones **3** by the $Yb(OTf)_3$-catalyzed *cyclo*-condensation of 2-aminobenzamides **1** with 1,3-diketones (*β*-diketones) **2** under mild and neutral reaction conditions (Scheme 1). For example, the reaction of **1a** (X = H) with pentane-2,4-dione ($R^1 = R^2 = CH_3$) **2a** gave 2-methyl-4(3*H*)-quinazolinone **3a** in high yield. The present reaction is surprising, but can be explained by assuming the formation of 1,2-dihydroquinazolone intermediates and the subsequent decomposition of 1,2-dihydroquinazolones by the $Yb(OTf)_3$-assisted cleavage of a C-C bond (Scheme 1, *vide infra*), which is a reminiscent of the McLafferty rearrangement in mass spectroscopy.[8]



Scheme 1. $Yb(OTf)_3$-catalyzed synthesis of 2-substituted 4(3*H*)-quinazolinones **3** from the *cyclo*-condensation of 2-aminobenzamides **1** and 1,3-diketones **2** via cleavage of a C-C bond

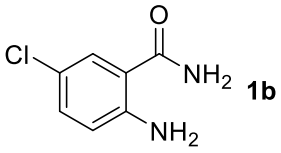
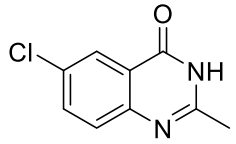
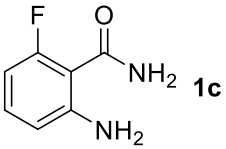
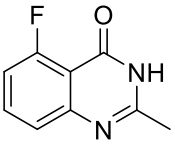
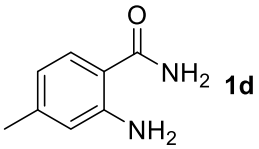
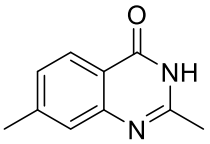
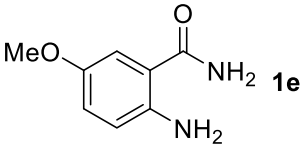
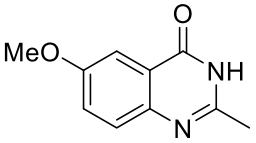
First, we examined the catalytic activities of several metal triflates and typical Lewis acids in the model reaction of 2-aminobenzamide **1a** with pentane-2,4-dione **2a** in mesitylene at 60 °C for 24 h under an argon atmosphere. The results are summarized in Table 1. Among the catalysts examined, $Yb(OTf)_3$ was the best, and gave 2-methyl-4(3*H*)-quinazolinone (**3a**) in 93% yield. In addition to $Yb(OTf)_3$, $Sc(OTf)_3$ showed high catalytic activity (**3a**, 92%), and other metal triflates showed moderate catalytic activity. However, $YbCl_3$ and $Yb(OAc)_3{\cdot}4H_2O$ showed moderate to low catalytic activity to give **3a** in respective yields of 78% and 21%, probably due to the weak coordination ability of chloro- and acetato-ligands to the ytterbium center. When the reaction was carried out in the presence of a catalytic amount of Brønsted acid such as CF_3SO_3H in place of $Yb(OTf)_3$ catalyst, the yield of **3a** decreased to 47%.

Table 1. Catalytic activity of several metal triflates and typical Lewis acid for the synthesis of **3a** from **1a** and **2a**[a]

entry	Lewis acid	yield of **3a** (%)[b]
1	—	2
2	$Yb(OTf)_3$	93
3	$Sc(OTf)_3$	92
4	$Y(OTf)_3$	66
5	$Sm(OTf)_3$	70
6	$Al(OTf)_3$	69
7	$Fe(OTf)_3$	65
8	$Cu(OTf)_2$	66
9	$Zn(OTf)_2$	68
10	$AlCl_3$	56
11	$FeCl_3$	33
12	$YbCl_3$	78
13	$Yb(OAc)_3{\cdot}4H_2O$	21
14	TfOH	47

[a] **1a** (1.0 mmol), **2a** (1.5 mmol), catalyst (0.050 mmol) in mesitylene (2.0 mL) at 60 °C for 24 h under an Ar atmosphere. [b] Determined by GLC.

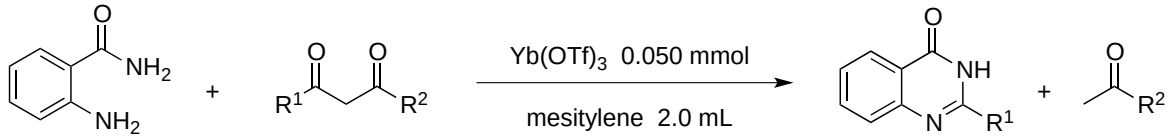
Table 2. Synthesis of 2-methyl-4(3*H*)-quinazolinones **3b-e** by $Yb(OTf)_3$-catalyzed *cross*-condensation of 2-amino-benzamides **1b-e** with pentane-2,4-dione **2a**[a]

entry	2-aminobenzamides **1**	isolated yield of 2-methyl 4(3*H*)-quinazolinone **3** (%)
1	 **1b**	 **3b**, 81
2	 **1c**	 **3c**, 92
3	 **1d**	 **3d**, 85
4	 **1e**	 **3e**, 94

[a] **1** (1.0 mmol), **2a** (1.5 mmol), $Yb(OTf)_3$ (0.050 mmol) in mesitylene (2.0 mL) at 60 °C for 24 h under an Ar atmosphere.

The present reaction occurred smoothly in several organic solvents such as mesitylene (**3a**, 93%), acetonitrile (90%), ethyl acetate (75%), THF (72%), and methanol (69%), and mesitylene was used as the best solvent for the following reactions.

Under the optimum reaction conditions, 2-aminobenzamides bearing several electron-withdrawing and electron-donating substituents on an aromatic ring (**1b-e**) were treated with **2a** and $Yb(OTf)_3$ catalyst in mesitylene at 60 °C for 24 h under an argon atmosphere to give the corresponding 2-methyl-4(3*H*)-quinazolinone derivatives (**3b-e**) in high isolated yields (Table 2).[9] All reactions of 2-aminobenzamide (**1a**) with various acyclic 1,3-diketones (**2a-c** and **2e**, R^1 = Me) by $Yb(OTf)_3$ catalyst gave 2-*methyl*-4(3*H*)-quinazolinone (**3a**) in high yields with high selectivity (Scheme 2). Similarly, methyl acetoacetate (**2d**), a *β*-keto ester, can be used in the present reaction to give 2-*methyl*-4(3*H*)-quinazolinone (**3a**) quantitatively.



1a 1.0 mmol

2a (R^1 = Me, R^2 = Me)
2b (R^1 = Me, R^2 = ^{t}Bu)
2c (R^1 = Me, R^2 = Ph)
2d (R^1 = Me, R^2 = OMe)
2e (R^1 = Me, R^2 = CF_3)
2f (R^1 = Et, R^2 = Et)
2g (R^1 = ^{t}Bu, R^2 = ^{t}Bu)
2h (R^1 = Ph, R^2 = Ph)
1.5 mmol

3a 93%
3a 96%
3a 90(87)%
3a 99%
3a 68%
3f (35)%
3g 66%
3h (53)%

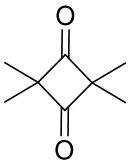
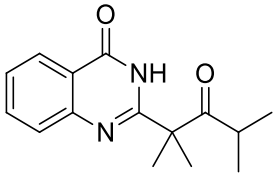
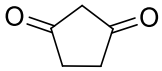
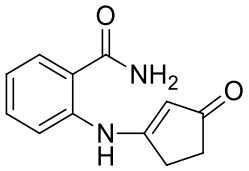
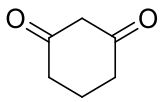
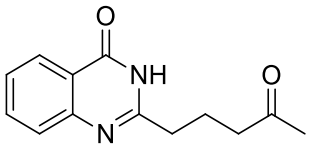
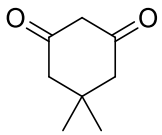
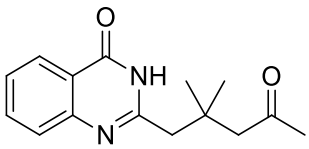
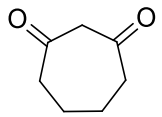
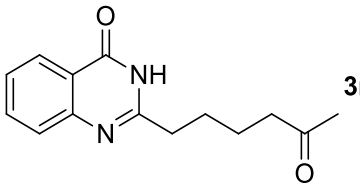
GLC yield (Figures in the parentheses are Isolated yield.)

Scheme 2. $Yb(OTf)_3$-catalyzed synthesis of 2-substituted 4(3*H*)-quinazolinones **3** from 2-aminobenzamide **1a** and 1,3-diketones (or *β*-ketoester) **2**

To obtain 4(3*H*)-quinazolinones bearing other alkyl substituents at the 2-position, symmetrically substituted 1,3-diketones such as heptane-3,5-dione (**2f**), 2,2,6,6-tetramethylheptane-3,5-dione (dipivaloylmethane) (**2g**), and 1,3-diphenylpropane-1,3-dione (**2h**) without an acetyl moiety (CH_3CO) to give 2-ethyl-, 2-(*tert*-butyl)-, and 2-phenyl-4(3*H*)-quinazolinone (**3f-h**) selectively in moderate to good yields. In addition, the products obtained by the $Yb(OTf)_3$-catalyzed *cyclo*-condensation reaction of 2-aminobenzamide (**1a**) with 1-phenylbutane-1,3-dione (**2c**) were analyzed carefully, and the formation of 2-methyl-4(3*H*)-quinazolinone (**3a**) in 90% yield and acetophenone in 65% yield was observed. This result is consistent with the proposed mechanism illustrated in Scheme 1 (*vide supra*) and Scheme 3 (*vide infra*).

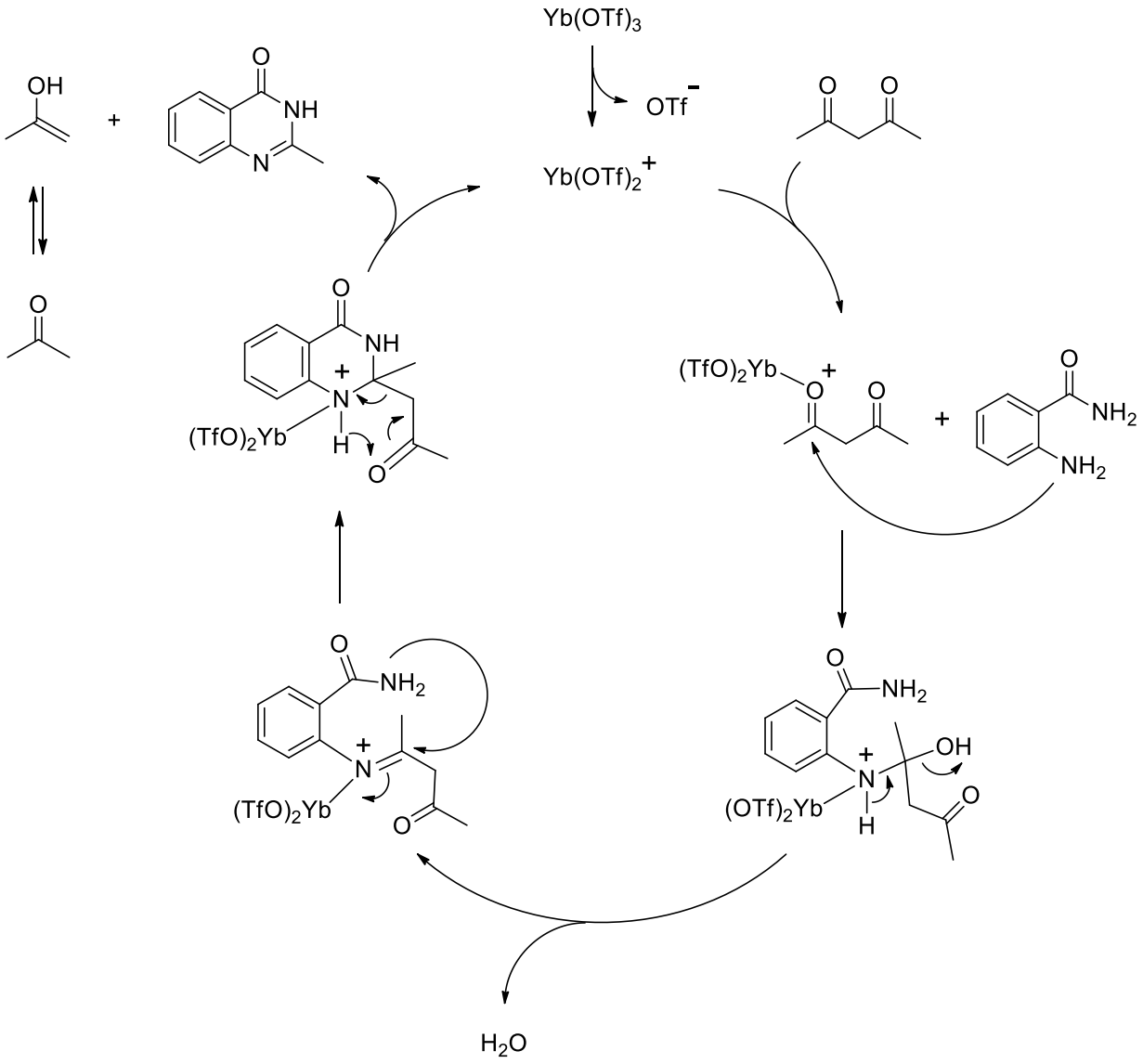
The reactions of 2-aminobenzamide (**1a**) with several cyclic 1,3-diketones (**2i**-**m**) were examined under the same optimum reaction conditions, and the results are summarized in Table 3. Except for **2j**, ring-opening and *cyclo*-condensation of cyclic 1,3-diketones (**2i** and **2k**-**m**) with **1a** gave the corresponding 2-(oxoalkyl)-4(3*H*)-quinazolinones (**3i** and **3k**-**m**) in good to high isolated yields. On the other hand, a five-membered cyclic 1,3-diketone, cyclopentane-1,3-dione (**2j**), gave a simple open-chain condensation product, 2-((3-cyclopent-1-en-1-yl)amino)benzamide **3j**, in 49% isolated yield without ring-opening, because of the high stability of an enol form of **2j**.

Table 3. Synthesis of 2-substituted 4(3*H*)-quinazolinones **3i-m** by the $Yb(OTf)_3$-catalyzed condensation of 2-aminobenzamide **1a** with cyclic 1,3-diketones **2i-m**[a]

entry	cyclic 1,3-diketones **2**		isolated yield of **3** (%)	
1		**2i**		**3i**, 56
2		**2j**		**3j**, 49
3		**2k**		**3k**, 75
4		**2l**		**3l**, 43
5		**2m**		**3m**, 52

[a] **1a** (1.0 mmol), **2** (1.5 mmol), $Yb(OTf)_3$ (0.050 mmol) in mesitylene (2.0 mL) at 60 °C for 24 h under an Ar atmosphere.

Based on a consideration of all of the results obtained above, the most plausible mechanism is illustrated in Scheme 3. We believe that the dissociation of a triflate anion OTf^- from $Yb(OTf)_3$ first occurs to generate catalytically active $Yb(OTf)_2^+$, which immediately coordinates to a carbonyl oxygen in 1,3-diketone. Subsequent nucleophilic attack of an amino group in 2-aminobenzamide to the activated carbonyl carbon in 1,3-diketone proceeds to give a hemiaminal intermediate, followed by migration of H^+ and dehydration to give an imine intermediate coordinated by $Yb(OTf)_2^+$. The intramolecular nucleophilic attack of an amino group to the imine carbon gives an aminal intermediate. Subsequent migration of H^+ and cleavage of a C-C bond assisted by coordinated $Yb(OTf)_2^+$ give 2-substituted 4(3*H*)-quinazolinone and an enol with the regeneration of catalytically active $Yb(OTf)_2^+$. The generated enol easily tautomerizes to the stable ketone.



Scheme 3. The most plausible mechanism

In conclusion, we have succeeded in developing a general, selective, and practical one-pot synthesis of 2-substituted 4(3*H*)-quinazolinones **3** by the $Yb(OTf)_3$-catalyzed *cyclo*-condensation of 2-aminobenzamides **1** with both acyclic and cyclic 1,3-diketones (*β*-diketones) **2** via the selective cleavage of a C-C bond in 1,3-diketones. A wide range of starting materials can be used in the present 4(3*H*)-quinazolinone synthesis, since the reaction proceeds smoothly under mild and neutral reaction conditions. Future studies on the use of $Yb(OTf)_3$ and other rare earth metal catalysts to construct valuable nitrogen-, oxygen-, and sulfur-containing heterocyclic compounds are in progress in our laboratory.

ACKNOWLEDGEMENTS

T.K. acknowledges financial support from the Asahi Glass Foundation and the Yazaki Memorial Foundation for Science and Technology. This research was conducted in part at the Katsura-Int'tech Center, Graduate School of Engineering, Kyoto University.

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8. F. W. McLafferty, *Mass Spectrometry of Organic Ions*, Academic Press. Inc., New York, 1963, p 337.
9. **General procedure for the synthesis of 2-substituted 4(3*H*)-quinazolinones 3:** A mixture of 2-aminobenzamide (**1**, 1.0 mmol), 1,3-diketone (**2**, 1.5 mmol), $Yb(OTf)_3$ (0.050 mmol, 5.0 mol%), and mesitylene (2.0 mL) was placed in a 20-mL Pyrex flask equipped with a magnetic stirring bar and a reflux condenser under a flow of argon. The reaction was carried out at 60 ºC (bath temp.) for 24 h with stirring. The reaction mixture was then cooled to room temperature and analyzed by GLC and GC-MS. The product **3** was isolated by medium-pressure column chromatography on silica gel (eluent: EtOAc/hexane = 30/70 ~ EtOAc 100%. For **3j**, eluent: MeOH/$CHCl_3$ = 30/70 ~ 50/50) and recrystallization from MeOH/hexane. The products **3l** and **3m** were isolated by recrystallization from EtOAc/hexane. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz in DMSO-d_6 (For **3j**, in a mixture of DMSO-d_6 and methanol-d_4). Elemental analyses were performed at the Microanalytical Center of Kyoto University. The analytical and spectral data of **3a**,[10] **3b-c**,[11] **3d**,[12] **3e**,[13] **3f**,[14] **3g-h**,[10] and **3j-l**,[7] are fully consistent with those reported previously. The products **3i**,[15] and **3m**[16] were characterized below.

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15. **3i**: a pale yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.03 (6H, d, J = 6.56 Hz), 1.51 (6H, s), 2.94-3.01 (m, 1H), 7.49 (1H, t, J = 7.34 Hz), 7.57 (1H, d, J = 7.80 Hz), 7.78 (1H, t, J = 8.30 Hz), 8.10 (1H, dd, J = 7.94 and 1.44 Hz), 12.04 (1H, br s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 20.6, 22.2, 35.8, 54.8, 120.9, 125.7, 126.6, 127.0, 134.5, 147.8, 158.8, 162.1, 213.5. MS (ESI): 259.4188(M+H)$^{+}$. *Anal*. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.62; H, 7.26; N, 10.71.
16. **3m**: a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.46-1.54 (2H, m), 1.64-1.71 (2H, m), 2.06 (3H, s), 2.46 (2H, t, J = 7.04 Hz), 2.57 (2H, t, J = 7.56 Hz), 7.44 (1H, t, J = 7.08 Hz), 7.57 (1H, d, J = 8.28 Hz), 7.75 (1H, t, J = 7.80 Hz), 8.06 (1H, dd, J = 7.80 and 1.48 Hz), 12.15 (1H, br s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 22.6, 26.2, 29.6, 34.2, 42.3, 120.7, 125.6, 125.9, 126.7, 134.2, 148.9, 157.2, 161.7, 208.3. MS (ESI): 245.1342(M+H)$^{+}$. *Anal*. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 59.93; H, 6.16; N, 9.54.