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$Yb(OTf)_3$-catalyzed cyclization of an *N*-silylenamine with 2-methylene-1,3-cyclohexanedione to afford a 7,8-dihydroquinolin-5(6*H*)-one derivative and its application to the one-pot conversion to a 2,3,5-trisubstituted quinoline derivative

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Abstract—A catalytic amount of ytterbium triflate ($Yb(OTf)_3$) promotes the cyclization of an *N*-silylenamine with in situ generated 2-methylene-1,3-cyclohexanedione and 2-methylenecyclohexanone to produce the corresponding 2,3-disubstituted 7,8-dihydroquinolin-5-one and 5,6,7,8-tetrahydroquinolin-5-one in moderate to good yields. A one-pot conversion of 7,8-dihydroquinolin-5-one to the quinoline derivative also proceeded in good yield.

A practical synthesis of polysubstituted quinolines and their dihydro/tetrahydro quinolines has attracted considerable interest in the fields of organic and pharmaceutical chemistry, since this basic skeleton is widespread in natural products and biologically active substances.[1] Hence, a number of methods, including the Conrad–Limpach–Knorr synthesis,[2] the Skraup synthesis,[3] and the Friedländer synthesis,[4] have been developed for the preparation of this skeleton. However, most of these classical methods generally require high temperatures and strong basic/acidic conditions, which may induce a decrease in product yield and the production of by-products via the polymerization of carbonyl components. Using a catalyst such as a Lewis acid, several groups have recently developed methods for the facile preparation of quinoline skeletons, which can be used under relatively mild conditions.[5] On the other hand, we previously reported on the cyclization of an *N*-silyl-1-azaallyl anion,[6] which can easily be generated from a functionalized silane and an aromatic nitrile in the presence of a base,[7] with 1,2-diketones, α,β-unsaturated ketones, and tropolones, leading to the preparation of heterocycles, such as pyrroles, pyridines, and azaazulenes.[8] During our continuing studies of the synthesis of heterocycles, we found that a combination of an *N*-silylenamine, formed by quenching the 1-azaallyl anion with water,[9] and an appropriate cyclic α,β-unsaturated compound leads to the production of quinoline skeletons (Scheme 1). We report herein on the $Yb(OTf)_3$-catalyzed cyclization of an *N*-silylenamine with 2-methylene-1,3-cyclohexanedione leading to a 2,3-disubstituted 7,8-dihydroquinolin-5(6*H*)-one derivative.[10] We also describe the efficient one-pot conversion to a 2,3,5-trisubstituted quinoline starting from the 2,3-disubstituted quinolin-5-one derivative.

We initially investigated the cyclization of *N*-silylenamine **1a**, prepared from a functionalized silane and benzonitrile in the presence of *n*-BuLi, with [(2,6-dioxocyclohexyl)methyl]dimethylammonium chloride[11] (**2a**), a 2-methylene-1,3-diketone precursor as a model reaction.[12] Table 1 shows the results of a search for optimized conditions. When conducted in THF, benzene, and acetonitrile, the reaction proceeded to produce the desired quinoline derivative **3aa**, but the yields were moderate (runs 1–3). Although DMSO showed a similar solvent effect for the cyclization, the use of DMF resulted in the production of a complex mixture (runs 4 and 5). Interestingly, when the reaction was run in

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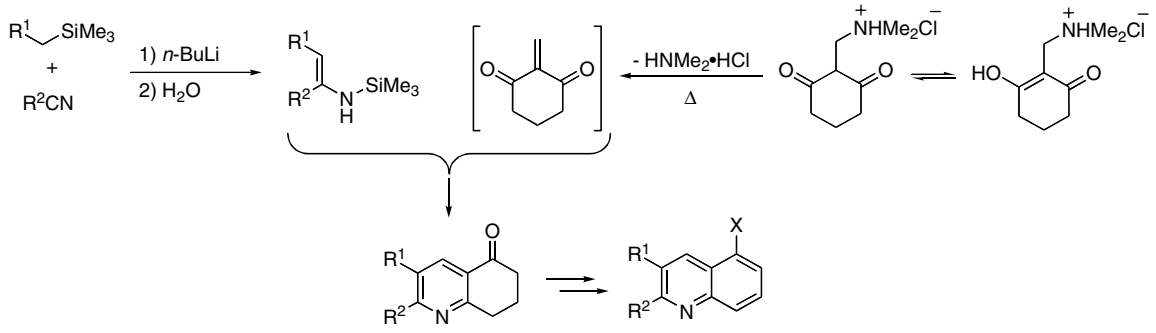
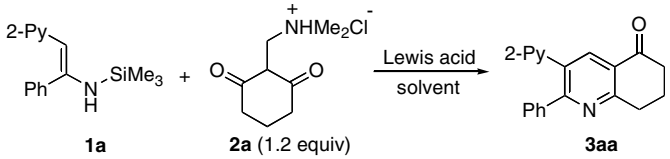


Scheme 1. Schematic method for quinoline synthesis by the cyclization of an *N*-silylenamine with 2-methylene-1,3-cyclohexanedione.

Table 1. Optimization of the cyclization of *N*-silylenamine **1a** with 2-methylene-1,3-cyclohexanedione precursor **2a**



1a **2a** (1.2 equiv) **3aa**

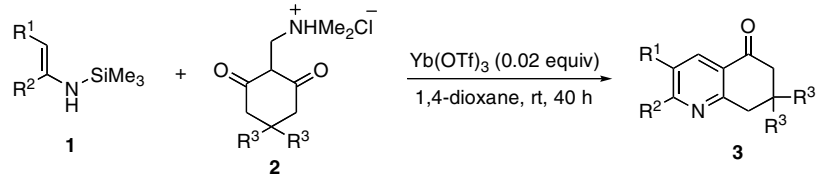
Run	Additive (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	—	THF	Reflux	12	32
2	—	PhH	Reflux	12	16
3	—	MeCN	Reflux	12	21
4	—	DMSO	100	12	38
5	—	DMF	100	12	ND
6	—	1,4-Dioxane	rt	12	69
7	$AlCl_3$ (0.2)	1,4-Dioxane	rt	40	37
8	$AlCl_3$ (0.2)	1,4-Dioxane	Reflux	40	73
9	$Hf(OTf)_4$ (0.2)	1,4-Dioxane	rt	40	75
10	$Yb(OTf)_3$ (0.2)	1,4-Dioxane	rt	40	78
11	$Yb(OTf)_3$ (0.2)	1,4-Dioxane	70	40	68
12	$Yb(OTf)_3$ (0.05)	1,4-Dioxane	rt	40	84
13	$Yb(OTf)_3$ (0.02)	1,4-Dioxane	rt	40	85

[a] NMR yields.

1,4-dioxane, the desired product **3aa** was formed at room temperature in 69% yield (run 6). Thus, to activate the carbonyl group of 2-methylene-1,3-cyclohexanedione generated in situ, we investigated the use of a Lewis acid as an additive. Among the compounds tested,[13] in case of $AlCl_3$, the reaction proceeded at room temperature, and the yield of **3aa** was increased to 73% under reflux (runs 7 and 8). It is noteworthy that, when the reaction was carried out in the presence of a catalytic amount of $Hf(OTf)_4$ or $Yb(OTf)_3$,[14] the cyclization also proceeded at room temperature to afford the corresponding quinolinone derivative **3aa** in good yield (runs 9 and 10). Surprisingly, even when the amount of the ytterbium catalyst was decreased to 0.05 or 0.02 equiv for the *N*-silylenamine, the catalyst showed a high catalytic activity and the product **3aa** was produced in excellent yield (runs 12 and 13). The structure of quinolinone **3aa** was confirmed by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.

To examine the general applicability of this cyclization, reactions of various *N*-silylenamines with two types of 2-methylene-1,3-cyclohexanedione (endione) precursors were carried out under the optimized conditions and the results are summarized in Table 2. The reaction of *N*-silylenamine **1b** containing an electron-donating group on the benzene ring with endione precursor **2a** produced the corresponding quinoline **3ba** in good yield (run 2). In contrast, the reaction of enamine **1c**, containing an electron-withdrawing group, resulted in a moderate yield, due to the reduced nucleophilicity of the enamine (run 3). When the reaction of **2a** with *N*-silylenamine **1d** containing an alkyl group as R^2 was conducted at room temperature, the product yield was low. However, at 60 °C, a satisfactory yield was obtained (run 4). Similarly, when the reaction of enamine **1e** with another heterocycle, such as a 3-methyl-5-isoxazolyl group with endione precursor **2b** having dimethyl groups was carried out at room temperature, the yield of product **3eb** was rather low. However, the yield was also improved to 60% when the reaction was run at 60 °C (run 8). Moreover, the reaction with an enamine having an ester or an amide group also gave the corresponding products in moderate to good yields (runs 9 and 10). For example, when the reaction of enamine **1f**, containing an *N*,*N*-dimethylamide group with an endione precursor was carried out under optimal conditions, the desired product **3fa** was obtained in 62% yield (run 9).

Table 2. $Yb(OTf)_3$-catalyzed cyclization of *N*-silylenamine **1** with the 2-methylene-1,3-cyclohexanedione precursor **2** leading to quinolinone derivative **3**[a]

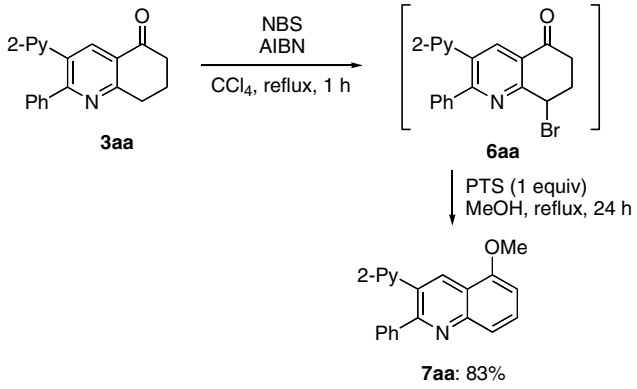


Run	*N*-Silylenamine **1**			1,3-Diketone **2**		Yield of **3** (%)	
	R^1	R^2		R^3			
1	2-Pyridyl	Ph	**1a**	H	**2a**	**3aa**	84
2	2-Pyridyl	4-MeO–C_6H_4	**1b**	H	**2a**	**3ba**	77
3	2-Pyridyl	4-Cl–C_6H_4	**1c**	H	**2a**	**3ca**	48
4	2-pyridyl	*n*-Bu	**1d**	H	**2a**	**3da**	34 (60)[b]
5	2-Pyridyl	Ph	**1a**	Me	**2b**	**3ab**	77
6	2-Pyridyl	4-MeO–C_6H_4	**1b**	Me	**2b**	**3bb**	51
7	3-Methyl-5-isoxazolyl	Ph	**1e**	H	**2a**	**3ea**	64
8	3-Methyl-5-isoxazolyl	Ph	**1e**	Me	**2b**	**3eb**	trace (60)[b]
9	$CONMe_2$	Ph	**1f**	H	**2a**	**3fa**	62
10	CO_2t-Bu	2-Pyridyl	**1g**	H	**2a**	**3ga**	36

[a] *N*-Silylenamine **1** (0.5 mmol), 2-methylene-1,3-diketone precursor **2** (1.2 equiv), and $Yb(OTf)_3$ (0.02 equiv) were used in 1,4-dioxane solution (1 mL).
[b] Reaction was carried out at 60 °C.

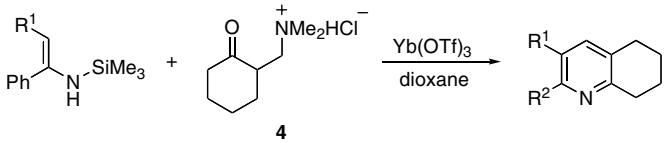
We then examined the cyclization of enamines with 2-methylene-1-cyclohexanone (enone) as a Michael acceptor; these reactions produced tetrahydroquinoline derivatives (Scheme 2). For example, when the reaction of *N*-silylenamine **1a** with enone precursor **4** was carried out at 60 °C for 30 h, the desired tetrahydroquinoline **5a** was produced in 57% yield. While the use of an *N*-silylenamine containing a 3-methyl-5-isoxazolyl group decreased the yield of **5e**.[15]

Finally, we examined the one-pot conversion[16] of the 7,8-dihydroquinolinone derivative **3aa** to quinoline derivative **7aa**. Quinolinone **3aa** was treated with *N*-bromosuccinimide (NBS) in the presence of 2,2′-azobis(isobutyronitrile) (AIBN) producing 8-brominated quinolinone **6aa**, followed by the treatment with *p*-toluenesulfonic acid in methanol without further purification, leading to the production of the corresponding 2,3,5-trisubstituted quinoline **7aa** in 83% yield (Scheme 3).[17]

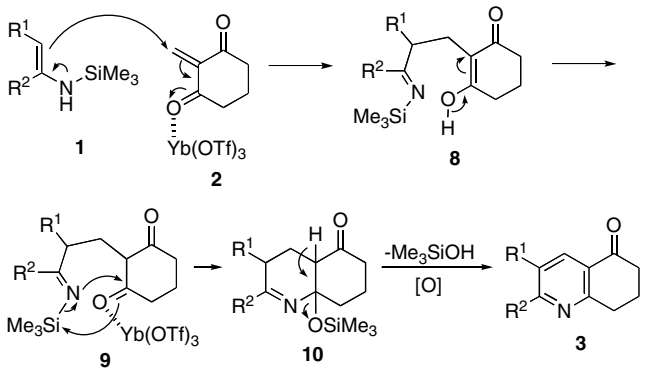


Scheme 3. One-pot conversion to the quinoline derivative starting from the quinolinone derivative.

A plausible mechanism for the cyclization of the enamine with 2-methylene-1,3-cyclohexanedione in the presence of $Yb(OTf)_3$ is shown in Scheme 4. Nucleophilic attack of the β-carbon of the enamine on the β-position of the α,β-unsaturated carbonyl group, which is activated by the ytterbium salt, initially occurs to produce intermediate **8**, followed by an in situ keto-enol isomerization to form the corresponding diketone intermediate **9**. An intramolecular attack of nitrogen atom in intermediate **9** on the activated carbonyl group then occurs to give the cyclization product **10**, followed by the elimination of silanol from **10** and subsequent oxidation, forming the desired quinolinone product **3**. The reaction



Scheme 2. Cyclization of *N*-silylenamine **1** with 2-methylene-1-cyclohexanone precursor **4**.



Scheme 4. Plausible mechanism for the cyclization of the *N*-silylenamine with 2-methylene-1,3-cyclohexanedione.

mechanism is analogous to that for the synthesis of pyridine from the N-silylenamine with α,β-unsaturated ketones.[8b,18]

In summary, we demonstrate that the $Yb(OTf)_3$-catalyzed cyclization of an *N*-silylenamine with in situ generated 2-methylene-1,3-cyclohexanedione and 2-methylenecyclohexanone leads to a 7,8-dihydroquinolin-5-one derivative. The ytterbium salt functions as a good catalyst, permitting the reaction to proceed under mild conditions. We also succeeded in the one-pot conversion of the quinolin-5-one derivative to the 2,3,5-trisubstituted quinoline derivative in good yield.

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References and notes

1. (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science Ltd: Oxford, 2000; pp 121–150; (b) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, pp 245–300; (c) Erian, A. W. *Chem. Rev.* **1993**, *93*, 1991.
2. For selected papers for the reactions from arylamines and 1,3-dicarbonyl compounds, see: (a) Tanyeli, C.; Akhmedov, I. M.; Isik, M. *Tetrahedron Lett.* **2004**, *45*, 5799; (b) Curran, A. C. W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 975.
3. For selected papers for the reactions from arylamines and α,β-unsaturated carbonyl compounds (a) Kobayashi, K.; Takanohashi, A.; Watanabe, S.; Morikawa, O.; Konishi, H. *Tetrahedron Lett.* **2000**, *41*, 7657; (b) Robinson, J. M.; Brent, L. W.; Chau, C.; Floyd, K. A.; Gillham, S. L.; McMahan, T. L.; Magda, D. J.; Motycka, T. J.; Pack, M. J.; Roberts, A. L.; Seally, L. A.; Simpson, S. L.; Smith, R. R.; Zalesny, K. N. *J. Org. Chem.* **1992**, *57*, 7352.
4. For selected papers for the reactions from *o*-acylarylamines and α-methylene carbonyl compounds, see: (a) Yadav, J. S.; Reddy, B. V. S.; Premalatha, K. *Synlett* **2004**, 963; (b) Breitmaier, E.; Gassenmann, S.; Bayer, E. *Tetrahedron* **1970**, *26*, 5907; (c) Breitmaier, E.; Bayer, E. *Tetrahedron Lett.* **1970**, *11*, 3291; (d) Breitmaier, E.; Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 765; (e) Fehnel, E. A. *J. Org. Chem.* **1966**, *31*, 2899.
5. (a) De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 1647; (b) Theoclitou, M.-E.; Robinson, L. A. *Tetrahedron Lett.* **2002**, *43*, 3907; (c) Jiang, B.; Si, Y.-G. *J. Org. Chem.* **2002**, *67*, 9449.
6. Mangelinckx, S.; Giubellina, N.; Kimpe, N. D. *Chem. Rev.* **2004**, *104*, 2353.
7. Konakahara, T.; Murayama, T.; Sano, K.; Kubota, S. *J. Chem. Res. (S)* **1996**, 136.
8. (a) Sakai, N.; Hattori, N.; Tomizawa, N.; Abe, N.; Konakahara, T. *Heterocycles* **2005**, *65*, 2799; (b) Konakahara, T.; Sugama, N.; Yamada, A.; Kakehi, A.; Sakai, N. *Heterocycles* **2001**, *55*, 313; (c) Konakahara, T.; Ogawa, R.; Tamura, S.; Kakehi, A.; Sakai, N. *Heterocycles* **2001**, *55*, 1737; (d) Hojahmat, M.; Konakahara, T.; Tamura, S. *Heterocycles* **2000**, *53*, 629; (e) Konakahara, T.; Watanabe, A.; Maehara, K.; Nagata, M.; Hojahmat, M. *Heterocycles* **1993**, *35*, 1171.
9. Konakahara, T.; Sato, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1241.
10. For selected reviews and paper of a reaction using $Yb(OTf)_3$, see: (a) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227; (b) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357; (c) Kobayashi, S. *Synlett* **1994**, 689.
11. Sielemann, D.; Keuper, R.; Risch, N. *Eur. J. Org. Chem.* **2000**, 543.
12. General procedure for the preparation of 7,8-dihydroquinolin-5-one **3**: To a 1,4-dioxane solution (1 mL) of [(2,6-dioxocyclohexyl)methyl]dimethylammonium chloride (**2a**, 125 mg, 0.60 mmol) and *N*-silylenamine **1** (0.50 mmol) was added $Yb(OTf)_3$ (6.2 mg, 0.010 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 40 h and its progress was monitored by TLC. To quench the reaction, H_2O (2 mL) was added to the mixture. After the usual work-up, the crude product was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give 7,8-dihydroquinolin-5-one **3**. Spectral data for selected novel compounds: 7,8-dihydro-7,7-dimethyl-2-phenyl-3-(2-pyridinyl)-quinolin-5(6*H*)-one (**3ab**); white solid; mp 160–162 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.58 (m, 1H), 8.50 (s, 1H), 7.43–6.95 (m, 8H), 3.08 (s, 2H), 2.53 (s, 2H), 1.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.6, 161.7, 161.1, 157.2, 149.8, 139.3, 137.2, 135.8, 134.1, 129.7, 128.7, 128.1, 125.6, 124.8, 122.1, 52.1, 46.4, 33.0, 28.3; MS (FAB) *m*/*z* 329 (M+H, 100%); Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.17; H, 6.13; N, 8.55; 7,8-dihydro-3-(3-methyl-5-isoxazolyl)-2-phenylquinolin-5(6*H*)-one (**3ea**); white solid; mp 133–134 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.67 (s, 1H), 7.41 (m, 5H), 5.55 (s, 1H), 3.22 (t, 2H, J = 6.5 Hz), 2.74 (t, 2H, J = 6.5 Hz), 2.24 (q, 2H, J = 6.5 Hz), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.9, 166.7, 163.9, 160.8, 159.9, 139.0, 135.7, 129.4, 128.6, 128.5, 126.5, 121.6, 104.4, 38.5, 32.6, 21.6, 11.4; MS (FAB) *m*/*z* 305 (M+H, 100%); Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.48; N, 9.20. Found: C, 74.96; H, 5.48; N, 9.20; 5,6,7,8-tetrahydro-2-phenyl-3-(2-pyridinyl)quinoline (**5aa**); white solid; mp 126–127 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.67 (m, 1H), 7.71 (s, 1H), 7.38–6.88 (m, 8H), 3.04 (t, 2H, J = 7.0 Hz), 2.87 (t, 2H, J = 7.0 Hz), 1.95 (q, 2H, J = 7.0 Hz), 1.86 (q, 2H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 157.0, 154.1, 149.4, 140.1, 138.7, 135.1, 132.1, 130.7, 129.5, 127.8, 127.4, 125.0, 121.3, 32.3, 28.1, 22.9, 22.5; MS (FAB) *m*/*z* 287 (M+H, 100%);

HRMS (FAB): Calcd for $C_{20}H_{19}N_2$: 287.1548. Found 287.1540 (M+H).

13. Typical Lewis acids, such as $MgBr_2$, $ZnCl_2$, $EtAlCl_2$, and $InCl_3$ were ineffective for the reaction.
14. A reaction with 2 mol % of $Hf(OTf)_4$ resulted in 75% of the product yield.
15. Although the reaction of enamine **1e** with the enone precursor **4** ran at 60 °C for 24 h, the product yield of **5e** was not improved (25%).
16. Procedure for the one-pot preparation of quinoline **7aa**: To a carbon tetrachloride solution (1 mL) of NBS (59 mg, 0.33 mmol), and AIBN (1 mg, 0.006 mmol) was added dihydroquinolinone **3aa** (100 mg, 0.330 mmol) and the mixture was refluxed. After 45 min, the reaction mixture was cooled to room temperature, and methanol (4 mL) and *p*-toluenesulfonic acid monohydrate (63 mg, 0.33 mmol) were added and the solution was refluxed for a further 24 h. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (hexane/AcOEt = 1:1) to give 5-methoxy-2-phenyl-3-(2-pyridinyl)quinoline (**7aa**) as a white solid (86 mg, 83%); mp 147–149 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.83 (s, 1H), 8.62 (m, 1H), 7.73–6.81 (m, 11H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.3, 158.2, 155.6, 149.7, 148.5, 140.5, 135.5, 133.5, 132.6, 130.1, 129.9, 128.1, 128.1, 125.3, 121.7, 119.6, 104.4, 55.7; MS (FAB) *m*/*z* 313 (M+H, 100%); HRMS (FAB): Calcd for $C_{21}H_{17}N_2O$: 313.1341. Found 313.1334 (M+H).
17. Akbarzadeh, T.; Shafiee, A. *Synth. Commun.* **2004**, *34*, 1455.
18. (a) Konakahara, T.; Hojahmat, M.; Tamura, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2803; (b) Konakahara, T.; Mojahmat, M.; Sujimoto, K. *Heterocycles* **1997**, *45*, 271.