Reaction of Imidoformates with Anthranilates: Facile, One-Pot, Three-Component Synthesis of 8*H*-Quinazolino[4,3-b]quinazolin-8-ones [1]

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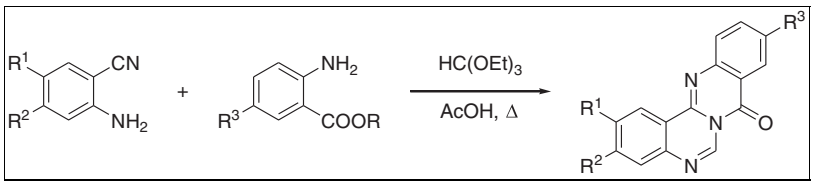
Received August 29, 2011
DOI 10.1002/jhet.1603
Published online 00 Month 2013 in Wiley Online Library (wileyonlinelibrary.com).



We report a facile, one-pot, three-component methodology for the synthesis of 8*H*-quinazolino[4,3-b]quinazolin-8-ones from commercially available 2-aminobenzonitriles, triethyl orthoformate, and anthranilic acids/esters/amides in good yields.

J. Heterocyclic Chem., **00,** 00 (2013).

INTRODUCTION

Over the past decade, the synthesis of heterocycles has become the cornerstone of synthetic organic chemistry as a result of a wide variety of applications of these heterocycles in medicinal and pharmaceutical chemistry [2]. The exploration of heterocycles as privileged structures in drug discovery is, beyond doubt, one of the major areas in medicinal chemistry [3]. In these, quinazoline ring system is a ubiquitous structural unit found in a number of alkaloids and many biologically active compounds [4]. The quinazolinone moiety is an important pharmacophore showing a number of pharmacological activities. Among this class of molecules, 4-anilinoquinazolines have been shown to possess EGFR (epidermal growth factor receptor) tyrosine kinase inhibitory effects, useful to inhibit tumor growth [5]. For example, Iressa (**1**) and Tarceva (**2**; Fig. 1) are two selective EGFR-TK inhibitors approved by the FDA in 2004 for locally advanced or metastatic non-small cell lung cancer (NSCLC) therapy and are currently under evaluation in clinical trials for other tumors. The quinazoline-fused nitrogen-heterocyclic unit, such as 8*H*-quinazolino[4,3-b]quinazolin-8-ones, has received little attention [6–9] and its biological activities are not evaluated. Multicomponent reactions (MCRs) have manifested as a powerful tool for the rapid introduction of molecular diversity. The design and development of MCRs for the generation of heterocycles receive growing interest [10].

Because of our interest in bio-active heterocycles for cancer, we are interested in the synthesis and evaluation of fused quinazolines. Herein, we describe a facile, one-pot, three-component synthesis of 8*H*-quinazolino[4,3-b]quinazolin-8-ones.

RESULTS AND DISCUSSION

Synthesis of the 8*H*-quinazolino[4,3-b]quinazolin-8-one skeleton was rarely studied [6–9]. The known methods to access these nitrogen heterocycles rely on multistep chemical transformations. For example, two-step conversion of anthranilic acid into 4-chloroquinazoline (**3**) via 4-(3*H*)-quinazolinone [11] followed by its reaction with either anthranilic acid or its ester generates 8*H*-quinazolino[4,3-b]quinazolin-8-one [6,7], whose efficiency has been increased by employing microwave irradiation technique [8]. Another method involves the samarium iodide-promoted intramolecular cascade radical cyclization of cyanamide radical precursor **4**, which was prepared in three steps from 2-iodoaniline [8] (Scheme 1). Furthermore, these known methods involve a series of reactions and the use of corrosive chemicals such as thionyl chloride/phosphoryl chloride and costly reagents such as samarium iodide.

During the course of synthesis of novel analogues for cancer, we were surprised to find that the reaction of imidoformate [12] with methyl anthranilate produces 8*H*-quinazolino[4,3-b]quinazolin-8-one (**5**) in moderate yield. The structure of the product has been deduced from its spectroscopic data and finally confirmed by comparing with that described in the literature [8,9]. To find the best conditions for this new reaction, we have selected imidoformate **7a**, which was prepared from 2-aminobenzonitrile (**6a**) and triethyl orthoformate in presence of acetic acid. Then the imidoformate **7a** was treated with methyl anthranilate under various conditions and the results were summarized in Table 1. First, the reaction was examined under protic and aprotic solvents; however, no reaction was observed (Table 1, entries 1–3). We were pleased to observe that, with acetic acid as solvent at RT, the reaction provided the highest yield

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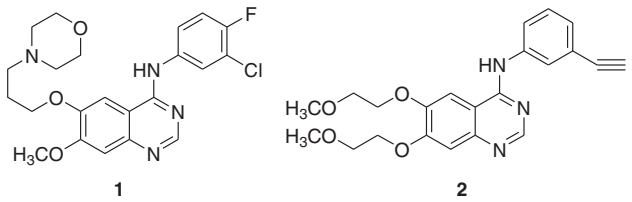


Figure 1. Chemical structures of Iressa (**1**) and Tarceva (**2**).

(65%) of **5a** after 1 h (entry 4). When acetic acid was replaced with trifluoroacetic acid or HCl, the reaction did not proceed but the imidoformate **7a** was completely decomposed (entries 6 and 11). It was also observed that the reaction proceeded with 1 equivalent of acetic acid and toluene as a solvent in 55% yield (entry 8). The reaction did not proceed in basic conditions such as K_2CO_3 and triethylamine (entries 14 and 15).

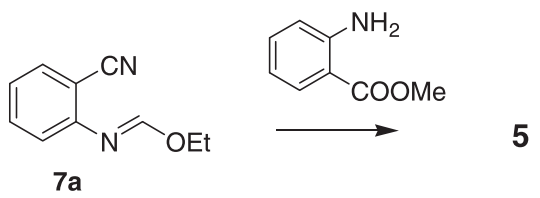
Encouraged by the aforementioned results, we tried one-pot procedure to make **5** from readily available 2-aminobenzonitriles and anthranilic acid esters. Thus, 2-aminobenzonitrile (**6a**) was treated with triethyl orthoformate in toluene to produce imidoformate derivative **7a**. Without purification, the imidoformate **7a** was treated with acetic acid and methyl anthranilate to produce **5a**, in good yield (Scheme 2).

The generality of the methodology has been established and generated substituted 8*H*-quinazolino[4,3-b] quinazolin-8-ones **5a–5g**, summarized in table 2. A wide variety of substituents on the 2-aminobenzonitrile and anthranilates were tolerated including methoxy, methyl, and halogens. We also tried the same procedure using various esters such as methyl anthranilate (entry 1) and ethyl anthranilate (entry 2) with same yields of the product. All the products have been characterized by their analytical and spectroscopic data. Further, the purity of the compounds has been established by high performance liquid chromatography (HPLC). Quite expectedly, the reaction was found to proceed not only with esters (entries 1–8) but also with anthranilic acids (entries 9–15) with equal efficiency.

The procedure was also applicable to anthranilamide instead of anthranilates and gave same yield of the products.

Table 1

Optimization[a] of **5** from imidoformate **7a**.



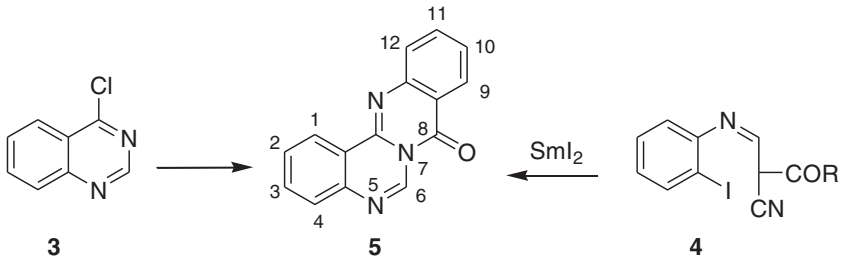
Entry	Solvent	Acid/ base	Temp. (°C)/time (h)	Yield[b] (%)
1	Toluene	—	Reflux/1	NR
2	DMF	—	130–140/1	NR
3	DMSO	—	130–140/1	NR
4	—	AcOH	RT/1	65
5	—	AcOH	Reflux/0.5	64
6	—	TFA	RT/16	NR
7	CH_3CN	AcOH	Reflux/1	43
8	Toluene	AcOH	RT/2	55
9	Toluene	AcOH	Reflux/1	44
10	DMF	AcOH	Reflux/5	10
11	DMF	HCl	RT/16	NR
12	DMSO	AcOH	Reflux/3	5
13	Ethanol	AcOH	Reflux/1	10
14	DMF	K_2CO_3	130–140/1	NR
15	Toluene	TEA	Reflux/2	NR

[a]Reaction conditions: imidoformate **7a** (1.0 equiv), methyl anthranilate (1.2 equiv), solvent, and/or acid/base.
[b]Isolated yield.

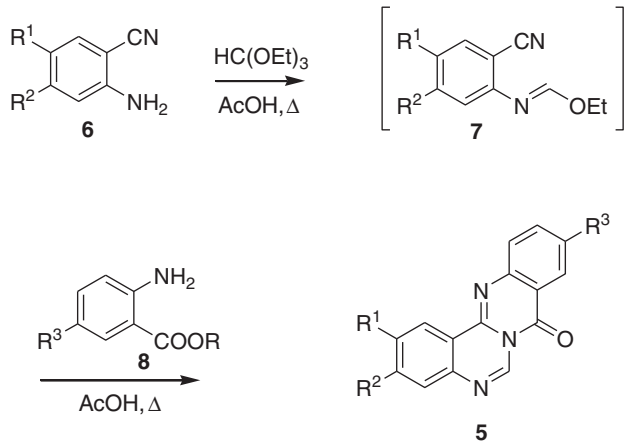
Thus, 2-aminobenzonitrile (**6a**) was treated with triethyl orthoformate followed by anthranilamide at RT to produce **5a**, in 60% yield. However, using the same procedure with anthranilonitrile instead of anthranilates did not give the product **5**.

A tentative mechanism via Dimroth rearrangement is given in Scheme 3. The first step involved the formation of imidoformate derivative **7** from 2-aminobenzonitrile and triethyl orthoformate in presence of acetic acid, which was then added to methyl anthranilate (**8**) to give **9**. Hydrolysis of the pyrimidine ring of **9** with subsequent rotation of 180° and ring closure gives 4-anilinoquinazoline derivative **10** [13] and further undergoes

Scheme 1. Known methods to prepare **5**.



Scheme 2. One-pot synthesis of 8*H*-quinazolino[4,3-b]quinazolin-8-ones (**5**).



5a: $R^1=R^2=R^3=H$

5b: $R^1=R^2=OCH_3$; $R^3=H$

5c: $R^1=R^2=H$; $R^3=CH_3$

5d: $R^1=R^3=H$; $R^2=Cl$

5e: $R^1=R^2=OCH_3$; $R^3=Br$

5f: $R^1=R^2=OCH_3$; $R^3=Cl$

5g: $R^1=R^2=OCH_3$; $R^3=CH_3$

Table 2

One-pot synthesis of **5**.

Entry	6			8	Product	Yield[a] (%)
	R^1	R^2	R	R^3		
1	H	H	CH_3	H	**5a**	65
2	H	H	C_2H_5	H	**5a**	64
3	OCH_3	OCH_3	CH_3	H	**5b**	64
4	H	H	CH_3	CH_3	**5c**	69
5	H	Cl	CH_3	H	**5d**	65
6	OCH_3	OCH_3	CH_3	Br	**5e**	66
7	OCH_3	OCH_3	CH_3	Cl	**5f**	62
8	OCH_3	OCH_3	CH_3	CH_3	**5g**	64
9	H	H	H	H	**5a**	53
10	OCH_3	OCH_3	H	H	**5b**	55
11	H	H	H	CH_3	**5c**	58
12	H	Cl	H	H	**5d**	55
13	OCH_3	OCH_3	H	Br	**5e**	56
14	OCH_3	OCH_3	H	Cl	**5f**	52
15	OCH_3	OCH_3	H	CH_3	**5g**	54

[a]Isolated yields.

intramolecular lactamization to give **5**. Attempts to isolate any of the intermediates by carrying out the reaction at low temperatures were unsuccessful.

CONCLUSIONS

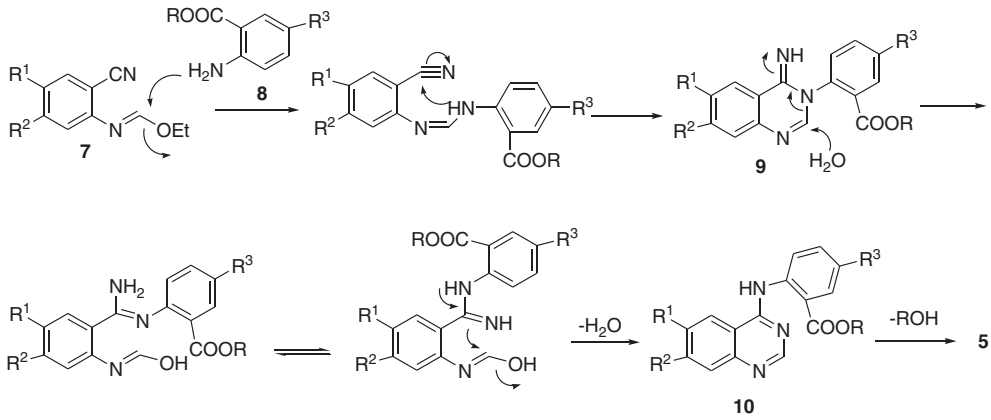
In conclusion, we have demonstrated the reaction of imidoformates with methyl anthranilate in presence of acetic acid for the formation of 8*H*-quinazolino[4,3-b] quinazolin-8-ones. To the best of our knowledge, this is the first report for the formation of these nitrogen heterocycles from imidoformates. This reaction opens the possibility of new synthetic routes to various heterocyclic compounds. Subsequently, the reaction has been utilized as a facile, three-component, one-pot synthesis of 8*H*-quinazolino[4,3-b]quinazolin-8-ones starting from readily available 2-aminobenzonitriles, triethyl orthoformate, and anthranilic acids/esters/amides. The generality of the methodology has been established and has several advantages, including simple conditions, easy workup, high yields, and commercially available starting materials and reagents. Further investigation into the mechanism and pharmacological activities of these nitrogen heterocycles is underway and will be reported in due course.

EXPERIMENTAL

Reagents and all solvents were analytically pure grade and were used without further purification (Sigma-Aldrich, Bangalore, India). Anhydrous conditions were not required for this reaction. Melting points were recorded on a Mel-Temp melting point apparatus (Electrothermal, Iowa, USA), in open capillaries and were uncorrected. IR spectra were recorded on a Perkin-Elmer BX1 FTIR spectrophotometer (CT, USA). ^{1}H NMR (400 MHz), ^{13}C NMR-DEPT (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer (Switzerland). The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 spectra. Mass spectra were recorded on Agilent 1100 LC/MSD (USA). High resolution mass spectra were recorded on Micromass Q-TOF micro mass spectrometer using electro-spray ionization mode. HPLC was recorded by a Shimadzu SIL-20A instrument (Tokyo, Japan) under the following conditions: column, Phenomenex Luma C18; flow rate, 1 mL/min; detection at 280–360 nm and mobile phase, 0.1% phosphoric acid: acetonitrile.

Ethyl (2-cyanophenyl)imidoformate (7a). To a solution of 2-aminobenzenecarbonitrile (500 mg, 4.23 mmol) in toluene (15 mL) was added sequentially triethyl orthoformate (1.35 g, 9.15 mmol) and acetic acid (0.15 g, 2.5 mmol) at RT. The reaction mixture was stirred at 100–110°C for 3 h, and while stirring, ethanol was collected using the Dean–Stark apparatus. Toluene was evaporated under vacuum, and the residue was chromatographed over silica gel column using hexane-EtOAc (98:2) as eluent to give the product as a pale yellow color oil (730 mg, 99%) (literature [12a] oil). IR (neat) ν_{max} 2984, 2226, 1643, 1595, 1264, 1199, 1098, 1008, 895, 832, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (1H, s), 7.60 (1H, dd, J = 7.8, 1.4 Hz), 7.50 (1H, td, J = 7.8, 1.5 Hz), 7.17 (1H, td, J = 7.6, 0.8 Hz), 6.98 (1H, br d, J = 8.0 Hz), 4.42 (2H, q, J = 7.0 Hz),

Scheme 3. Proposed mechanism for the formation of **5**.



1.41 (3H, t, $J = 7.0$ Hz); LC-MS (positive ion mode): *m/z* 175 $(M+H)^+$.

General procedure for the one–pot synthesis of 5. To a solution of 2-aminobenzenecarbonitrile (5 mmol) in toluene (15 mL) was added sequentially triethyl orthoformate (10 mmol) and acetic acid (2.5 mmol) at RT. The reaction mixture was stirred at 100–105°C for 3 h, and while stirring, ethanol was collected using the Dean–Stark apparatus. Toluene was evaporated under vacuum. A solution of methyl anthranilate (6 mmol) in acetic acid (12 mL) was added to the aforementioned residue and the mixture was stirred at RT for 1 h and refluxed for 1 h. The mixture was poured into ice cold water, neutralized with ammonia, and stirred for 10 min. The precipitated solid was filtered, washed with water, dried, and further purified by column chromatography.

8H-Quinazolino[4,3-b]quinazolin-8-one (5a). Pale yellow color solid, mp 190–192°C (literature [9] mp 194–196°C); IR (KBr) ν_{max} 1704, 1625, 1460, 1377, 1326, 1262, 1245, 1140, 1023, 876, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.37 (1H, s), 8.75 (1H, d, $J = 8.0$ Hz), 8.37 (1H, d, $J = 8.0$ Hz), 7.74–7.86 (4H, m), 7.60 (1H, t, $J = 7.2$ Hz), 7.49 (1H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 147.6, 144.4, 143.1, 137.7, 135.8, 133.6, 128.8, 128.1, 127.7, 127.5, 126.5, 125.9, 121.4, 118.7; LC-MS (positive ion mode): *m/z* 248 $(M+H)^+$; HPLC: 99.44%.

2,3-Dimethoxy-8H-quinazolino[4,3-b]quinazolin-8-one (5b). Off-white color solid, mp 290–292°C (literature [8] mp >260°C); IR (KBr) ν_{max} 3431, 1690, 1628, 1602, 1555, 1286, 1240, 1213, 1148, 1111, 1019, 979, 861, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.40 (1H, s), 8.41 (1H, d, $J = 8.0$ Hz), 8.15 (1H, s), 7.81–7.88 (2H, m), 7.48 (1H, t, $J = 7.2$ Hz), 7.26 (1H, d, $J = 7.6$ Hz), 4.12 (3H, s), 4.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 154.4, 150.4, 148.1, 144.2, 139.3, 136.6, 135.7, 127.5, 127.3, 125.8, 118.1, 114.8, 109.0, 105.4, 56.5, 56.3; LC-MS (positive ion mode): *m/z* 308 $(M+H)^+$; HPLC: 99.57%.

10-Methyl-8H-quinazolino[4,3-b]quinazolin-8-one (5c). Pale yellow color solid, mp 212–214°C (literature [8] mp 211°C); IR (KBr) ν_{max} 1712, 1626, 1585, 1489, 1421, 1375, 1328, 1288, 1267, 1253, 1215, 1149, 1080, 941, 908, 842, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.37 (1H, s), 8.74 (1H, d, $J = 8.0$ Hz), 8.15 (1H, s), 7.58–7.80 (5H, m), 2.50 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 144.6, 142.7, 142.0, 136.8, 136.4, 135.8, 132.3, 127.8, 127.1, 126.6, 125.8, 124.7, 120.6, 117.5, 20.3; LC-MS (positive ion mode): *m/z* 262 $(M+H)^+$; HPLC: 99.68%.

3-Chloro-8H-quinazolino[4,3-b]quinazolin-8-one (5d). Pale yellow color solid, mp 234–236°C; IR (KBr) ν_{max} 3428, 1704, 1624, 1470, 1380, 1317, 1261, 1243, 1202, 1150, 1068, 844, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.43 (1H, s), 8.75 (1H, d, $J = 8.4$ Hz), 8.43 (1H, dd, $J = 8.0$, 0.8 Hz), 7.87–7.92 (1H, m), 7.83–7.85 (2H, m), 7.60 (1H, dd, $J = 8.6$, 1.8 Hz), 7.52–7.57 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 147.6, 144.1, 143.9, 139.9, 139.0, 136.0, 129.4, 127.9, 127.8, 127.7, 127.3, 126.8, 120.1, 118.8; LC-MS (positive ion mode): *m/z* 282, 284 $(M+H)^+$; HRMS-(EI) (*m/z*) $(M+H)^+$ calcd. for $C_{15}H_8ClN_3O$ 282.0434, found 282.0434; HPLC: 99.49%.

10-Bromo-2,3-dimethoxy-8H-quinazolino[4,3-b]quinazolin-8-one (5e). Pale yellow color solid, mp 264–266°C; IR (KBr) ν_{max} 1705, 1625, 1501, 1465, 1307, 1275, 1218, 1110, 1030, 986, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.32 (1H, s), 8.42 (1H, d, $J = 2.0$ Hz), 7.98 (1H, s), 7.85 (1H, dd, $J = 8.6$, 2.2 Hz), 7.60 (1H, d, $J = 8.8$ Hz), 7.18 (1H, s), 4.10 (3H, s), 4.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 154.6, 150.5, 146.9, 144.5, 139.4, 138.8, 136.3, 129.8, 129.1, 119.3, 119.0, 114.6, 109.0, 105.3, 56.5, 56.4; LC-MS (positive ion mode): *m/z* 386, 388 $(M+H)^+$; HRMS-(EI) (*m/z*) $(M+H)^+$ calcd. for $C_{17}H_{12}BrN_3O_3$ 386.0140, found 386.0144; HPLC: 98.65%.

10-Chloro-2,3-dimethoxy-8H-quinazolino[4,3-b]quinazolin-8-one (5f). Pale yellow color solid, mp 272–274°C; IR (KBr) ν_{max} 3428, 1695, 1625, 1572, 1394, 1276, 1219, 1118, 1030, 986, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.34 (1H, s), 8.28 (1H, d, $J = 1.6$ Hz), 8.02 (1H, s), 7.68–7.75 (2H, m), 7.20 (1H, s), 4.11 (3H, s), 4.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 154.6, 150.5, 146.6, 144.4, 139.3, 136.3, 136.1, 131.5, 128.9, 126.6, 118.9, 114.6, 109.0, 105.3, 56.5, 56.4; LC-MS (positive ion mode): *m/z* 342, 344 $(M+H)^+$; HRMS-(EI) (*m/z*) $(M+Na)^+$ calcd. for $C_{17}H_{12}ClN_3O_3Na$ 364.0465, found 364.0470; HPLC: 99.51%.

2,3-Dimethoxy-10-methyl-8H-quinazolino[4,3-b]quinazolin-8-one (5g). Pale yellow color solid, mp 306–308°C (decomp); IR (KBr) ν_{max} 1699, 1627, 1607, 1289, 1281, 1248, 1218, 1044, 875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.42 (1H, s), 8.21 (1H, br s), 8.17 (1H, s), 7.76 (1H, d, $J = 8.4$ Hz), 7.69 (1H, dd, $J = 8.2$, 1.4 Hz), 7.27 (1H, s), 4.13 (3H, s), 4.05 (3H, s), 2.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 154.2, 150.4, 146.2, 143.7,

139.1, 137.4, 136.8, 136.1, 127.2, 126.8, 117.9, 115.0, 109.1, 105.4, 56.5, 56.4, 21.3; LC-MS (positive ion mode): *m/z* 322 $(M+H)^+$; HRMS-(EI) (m/z) $(M+Na)^+$ calcd. for $C_{18}H_{15}N_3O_3Na$ 344.1011, found 344.1012; HPLC: 99.80%.

Acknowledgments. We sincerely thank Sri G. Ganga Raju, Chairman, and Mr. G. Rama Raju, Director, of Laila Impex for support and encouragement. We are also thankful to Prof. A. Srikrishna, Department of Organic Chemistry, Indian Institute of Science, Bangalore, India, for helpful discussions.

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