Articles

Intramolecular Cyclization of Azides by Iminium Species. A Novel Method for the Construction of Nitrogen Heterocycles under Vilsmeier Conditions

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An unprecedented attack of the azide functionality by iminium species, generated in situ under Vilsmeier conditions, provided a novel route for the construction of nitrogen heterocycles. Thus, the treatment of 2-azidoacetophenones with Vilsmeier reagent under reflux conditions gave 5-aryloxazole-4-carboxaldehydes. One-pot synthesis of oxazole carboxaldehydes from 2-bromoacetophenones by dehaloazidation−Vilsmeier cyclization reaction sequence provided better yields. The susceptibility of the carbonyl group to undergo chloroformylation at room temperature without affecting the azide function was exploited to provide an attractive scheme for the synthesis of α-azido-β-chlorovinyl azides from phenacyl azides. The synthesis of a series of *N*-aryl 5-chloro-2-(dimethylamino)imidazole-4-carboxaldehydes was accomplished by the Vilsmeier cyclization of *N*-aryl-2-azidoacetamides. The possible mechanisms for the reactions are also discussed.

Introduction

In recent times, there has been a growing interest in the area of application of azides in organic synthesis which could be attributed to the broad spectrum of reactivity of these versatile reagents.[1] The common types of reactions of azides which lead to the synthesis of heterocycles in which only one azide nitrogen is retained are reductive cyclization,[2] Staudinger reaction,[3] Curtius rearrangement,[4] Schmidt rearrangement,[5] nitrene insertion,[6] and radical cyclization.[7]

The cycloaddition of azides across a double bond provides a general synthetic approach to triazolines,[8] aziridines,[9] and other related heterocycles. The vinyl azides are highly reactive and are susceptible to photolysis,[10] pyrolysis,[11] cycloadditions,[12] and attack by nucleophiles[13] as well as by electrophiles.[14] The electrophilic attack of the vinyl azide can either occur at the β-vinyl carbon[15] or at the α-nitrogen atom of the azide.[16] A survey of literature revealed that the electrophilic attack of the azides by iminium species is not explored to date. Toward this end, we analyzed a synthetic strategy for

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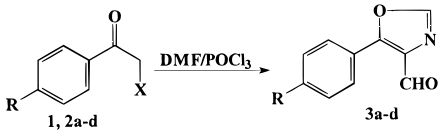
the construction of nitrogen heterocycles by the Vilsmeier cyclization of azides which consists of the following steps. (i) The in situ generation of iminium salt from a Vilsmeier-active functional group which is strategically located from the azide. (ii) The intramolecular cyclization of the azide by the iminium species followed by elimination of nitrogen.

The capability of Vilsmeier reagent to generate a broad spectrum of iminium species provides considerable scope and versatility for the intramolecular cyclization of azides by iminium species under Vilsmeier conditions. The reactive intermediates involved in the Vilsmeier−Haack−Arnold reaction are the halomethyleniminium salts derived from the action of acid chlorides on *N*,*N*-disubstituted formamides.[17] The classical Vilsmeier−Haack reaction involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt to yield the corresponding iminium species.[18] However, the scope of the reagent is not restricted to aromatic formylation. A wide variety of alkene derivatives,[19] carbonyl compounds,[20] activated methyl and methylene groups,[21] and oxygen[22] and nitrogen nucleophiles[23] react with Vilsmeier reagent to yield the corresponding iminium salts. The cyclization of iminium species under Vilsmeier conditions is an important synthetic tool of organic chemistry which provides a facile entry into large number of heterocyclic systems.[24] Recently, we have been focusing attention on exploiting the cyclization potential of this reagent.[25]

Scheme 1



We began our investigations by examining some of the general principles underlying the synthetic design of oxazolecarboxaldehydes from the corresponding 2-azidoacetophenones.[26] A one-pot synthetic strategy starting from the corresponding 2-bromoacetophenones involving a dehaloazidation−Vilsmeier cyclization reaction sequence also proved successful. The success of our strategy prompted us to extend the potential of Vilsmeier cyclization of azides for the synthesis of other nitrogen heterocycles.

The novelty of the entire process lies in the Vilsmeier cyclization of the azide, which, to the best of our knowledge, is unprecedented. A detailed account of our studies on the construction of nitrogen heterocycles and the possible reaction pathways are discussed in this paper.

Results and Discussion

Synthesis of Oxazoles. We envisaged that the Vilsmeier cyclization of 2-azidoacetophenones **1** would provide an efficient route for the preparation of 5-aryloxazole-4-carboxaldehydes **3**. The reaction was carried out at 80−90 °C for 2−3 h using 3 equiv of Vilsmeier reagent. Indeed, the reaction proceeded uneventfully, and the anticipated oxazoles were obtained in 36−45% yield (Scheme 1 and Table 1).

The prerequisite azidoacetophenones necessary for the oxazole synthesis were prepared in high yields from the corresponding 2-bromoacetophenones. The conversion was carried out in DMF using 2 equiv of NaN_3 at 15−20 °C for 20 min.

Sha et al.[27] have reported that alkyl azides generated in situ from the corresponding bromides undergo intramolecular cycloaddition to enones in DMF to provide a one-step synthesis of heterocycles. To enhance the utility of Vilsmeier cyclization, we examined a one-pot synthetic strategy of oxazolecarboxaldehydes directly from 2-bromoacetophenones **2**. This dehaloazidation−Vilsmeier cyclization protocol was prompted by the facile conversion of bromoacetophenones to the corresponding azidoacetophenones under mild conditions in DMF. The conversion was carried out using 1.1 equiv of NaN_3 and 6 equiv of $POCl_3$ in DMF. As expected the one-pot

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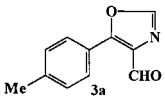
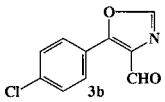
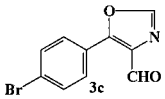
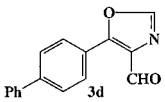
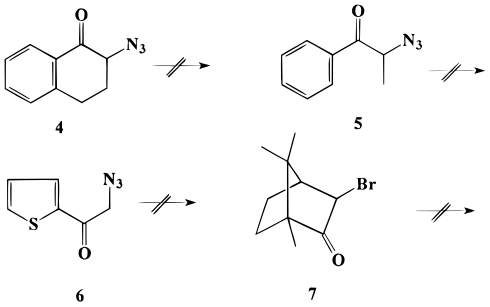
Table 1. Synthesis of Oxazoles from 2-Azidoacetophenones and 2-Bromoacetophenones Using Vilsmeier Reagent

Entry	Substrate	R	X	Product	Yield (%)	mp, °C
1	**1a**	Me	N_3		36	90
2	**2a**	Me	Br		45	
3	**1b**	Cl	N_3		36	130
4	**2b**	Cl	Br		48	
5	**1c**	Br	N_3		42	135
6	**2c**	Br	Br		56	
7	**1d**	Ph	N_3		45	160
8	**2d**	Ph	Br		61	

Scheme 2



strategy provided a convenient route to aryl oxazole carboxaldehydes, and the results are summarized in Scheme 1 and Table 1.

Thwarted Attempts at Cyclization. The attempted cyclization of 2-azidotetralone(**4**) and 2-azidopropiophenone(**5**) were thwarted by the formation of a complex mixture of products which could not be characterized by the conventional analytical techniques. Thus, the scope of the cyclization seems to be limited to 2-azidoacetophenones which are unsubstituted at 2-position.

2-(Azidoacetyl)thiophene (**6**) gave a resinous mass probably due to the competitive formylation of the active aromatic ring. Attempted cyclization of 2-bromocamphor (**7**) with 2 equiv of sodium azide and 6 equiv of Vilsmeier reagent under reflux conditions on a water bath for 10 h resulted only in the complete recovery of the starting material. These attempted cyclizations are represented in Scheme 2.

Synthesis of Vinyl Azides. Studies on the effect of temperature on cyclization provided some interesting results. The treatment of 2-azidoacetophenones with 6 equiv of Vilsmeier reagent at room-temperature resulted in the exclusive formation of products which exhibited strong IR absorption characteristic of azido group in the region ~2100 cm^{-1}. The products were confirmed to be 2-azido-3-chloro-3-aryl-2-propenals **8** by spectral data and elemental analysis. These vinyl azides could be stored

Scheme 3

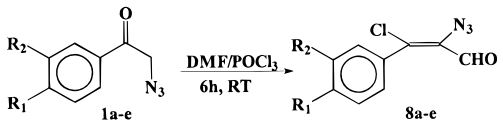


Table 2. Synthesis of α-Azido-β-chlorovinylaldehydes from 2-Azidoacetophenones Using Vilsmeier Reagent

entry	product	R_1	R_2	yield (%)	mp, °C
1	**8a**	Me	H	70	70
2	**8b**	Cl	H	62	98
3	**8c**	Br	H	65	104
4	**8d**	Ph	H	80	103
5	**8e**	H	Me	64	95

indefinitely without any apparent sign of decomposition below 5 °C.

Thus, the treatment of 2-azidoacetophenones with Vilsmeier reagent at room temperature provided a mild method for the generation of vinyl azides, and the results are summarized in Scheme 3 and Table 2. The chemical manipulation of various functional groups in the presence of an azide group is a field of current interest.[28]

Mechanistic Considerations. Vinyl azides upon pyrolysis normally decompose by loss of nitrogen from the azide with the formation of 2*H*-azirines. The azirine formation is followed by reversible thermal carbon−nitrogen bond cleavage to give the corresponding vinyl nitrenes, and hence the stereochemistry about the double bond of the azide is lost.[29] However, the mechanism for the interaction of azides with iminium species is not likely to involve the vinyl nitrene intermediate, first because the temperature employed in the reaction is too low to generate the nitrene and second the singlet nitrene is electrophilic in nature and is unlikely to attack an iminium species in preference to the azide.

Intramolecular cycloaddition of azide to a nitrile is reported to furnish tetrazole derivatives.[30] Imidoyl azides, usually generated in situ by the treatment of the corresponding chloride with azide, also undergo spontaneous cyclization to tetrazoles.[31] Taking into account all these considerations, a possible pathway for the thermal decomposition of 2-azidoacetophenones on treatment with Vilsmeier reagent is shown in Scheme 4. The chloromethyleniminium salt generated from DMF and $POCl_3$ reacts with the carbonyl group of **1** to yield the O-formylated species **9** which is in equilibrium with the chlorovinyl azide precursor **10**. The reaction at room temperature followed by aqueous workup yields the vinyl azide **8**. At 80−90 °C, the intermediate **9** undergoes a [3 + 2] dipolar cycloaddition of azide with the iminium ion to give the corresponding tetrazole intermediate **11**. Presumably, the intermediate **11** decomposes via loss of methyl proton to give nitrogen, $MeN{=}CH_2$, and oxazole carboxaldehyde **3**. Although the cyclization of azides by iminium species is unprecedented, a few reports are available on the cyclization of azides by imines.[32]

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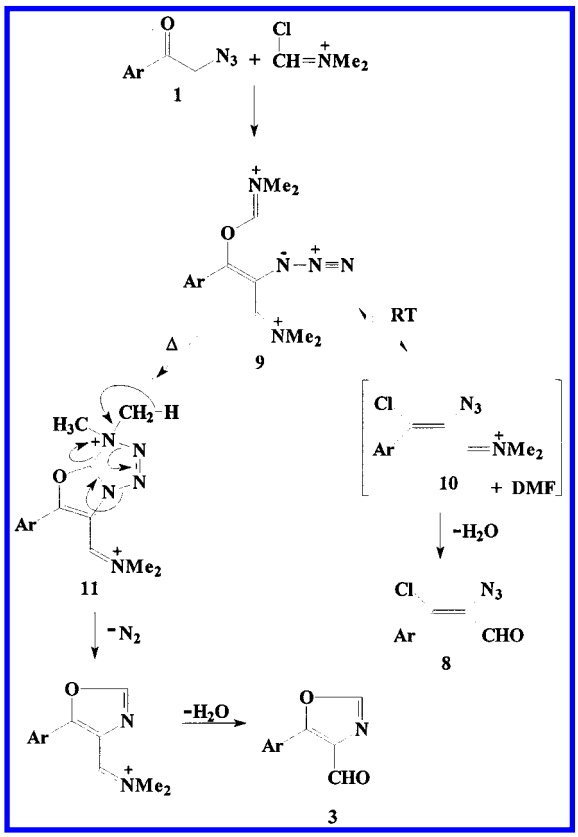
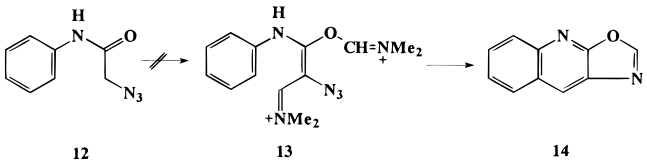
Scheme 4



Scheme 5



Synthesis of Imidazoles. The treatment of acyl anilides with Vilsmeier reagent is reported to provide an efficient route to the synthesis of 2-chloro-3-substituted quinolines by formylation of the side chain.[33] We have made an attempt to combine this feature with the Vilsmeier cyclization of azides to accomplish the synthesis of oxazole-fused quinolines **14** from *N*-aryl-2-azidoacetamides **12** as represented in the Scheme 5. Our synthetic strategy was prompted by the expectation that the major product might arise from the cascade cyclization of the intermediate **13**.

However, the reaction did not proceed as anticipated and instead gave 1-aryl-5-chloro-2-(dimethylamino)-1*H*-imidazole-4-carboxaldehydes **15** in good yields. Imidazole derivatives exhibit a broad spectrum of biological activities which include antimicrobial,[34a] antitumor,[34b] antiulcer,[34c] and antiaggregant properties[34d] and are used for asthma treatment.[34e] Imidazole derivatives also find applications as inhibitors of HIV virus,[34f] cytokine,[34g] and aldosterone.[34h] This prompted us to extend the reaction conditions further for the synthesis of various substituted imidazole chlorovinyl aldehydes from the corresponding

(32) (a) Ardakani, M. A.; Smalley, R. K. Smith, R. H. *Synthesis* **1979**, 308. (b) Ardakani, M. A.; Smalley, R. K. *Tetrahedron Lett.* **1979**, 4769. (c) Darwen, S. P.; Smalley, R. K. *Tetrahedron Lett.* **1985**, *26*, 5707. (d) Smalley, R. K.; Stocker, A. W. *Chem. Ind. (London)* **1984**, 222.

(33) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1520.

Scheme 6

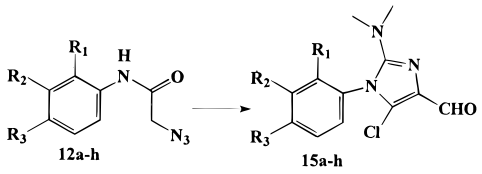
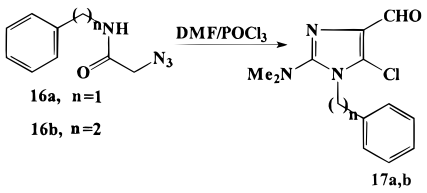


Table 3. The Formation of Imidazoles from 2-Azidoacetanilides Using Vilsmeier Reagent

entry	product	R_1	R_2	R_3	mp, °C	yield (%)[a]
1	**15a**	H	H	H	93	45
2	**15b**	H	H	Cl	100	48
3	**15c**	H	H	OCH_3	108	58
4	**15d**	H	Cl	H	119	39
5	**15e**	H	H	CH_3	123	62
6	**15f**	CH_2CH_3	H	H	*b*	36
7	**15g**	H	-CH=CH-CH=CH-		151	51
8	**15h**	CH_3	H	H	79	41

[a] The values represent isolated yield of the pure compounds after column separation. [b] The product **15f** separated out as highly viscous liquid.

Scheme 7



N-aryl-2-azidoacetamides and the results are summarized in the Scheme 6 and Table 3.

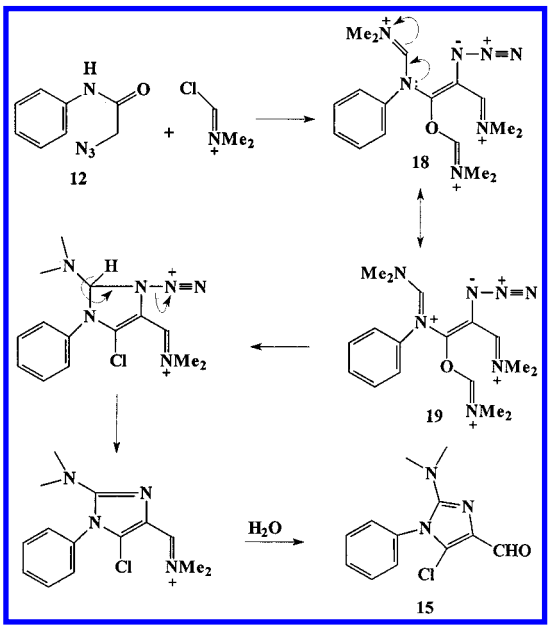
The synthesis of quinoline framework from acylanilides is reported to be favored by employing $POCl_3$ and DMF in a ratio of 7:3.[35] However, we observed that the nature of the cyclization product of *N*-aryl-2-azidoacetamides was not influenced by varying the ratio of reagent mixture. In general, better yields were obtained when 3 equiv of $POCl_3$ and 6 equiv of DMF were employed. No products bearing quinoline framework could be isolated under any of the reaction conditions adopted by us. 2-Azido-*N*-(phenylmethyl)acetamide **16a** and 2-azido-*N*-(2-phenylethyl)acetamide **16b** had also undergone cyclization on treatment with Vilsmeier reagent to yield the corresponding imidazoles **17a,b** in low yields (Scheme 7).

Mechanistic Considerations. The imidazole formation seems to proceed through the *N*-formylation ac-

(34) (a) For a recent review on imidazoles, see Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II*; Shinkai, I. Ed.; Elsevier: Oxford, UK, 1996; Vol. 3, p 77. (a) Hua, D. Y.; Zhang, F.; Chen, J. *J. Org. Chem.* **1994**, *59*, 5084. (b) Frei, J.; Stanek, J. PCT Int. Appl. WO 96 22, 979, 1996, 89 pp; *Chem. Abstr.* **1996**, *125*, 221842c. (c) Arakawa, E.; Kato, T.; Takamura, T.; Imai, K.; Segami, T.; Nakamura, Y. Eur. Pat. Appl. EP 728, 747, 1996, 53 pp; *Chem. Abstr.* **1996**, *125*, 221843d. (d) Linz, G.; Himmelsbach, F.; Pieper, H.; Austel, V.; Guth, B.; Weisenberger, J. PCT Int. Appl. WO 97 15, 567, 1997; *Chem. Abstr.* **1997**, *127*, 17681m. (e) Miller, S. C.; Jacobs, R. T.; Shenvi, A. B. Eur. Pat. Appl. EP 739, 831, 1996, 38 pp; *Chem. Abstr.* **1997**, *126*, 47220g. (f) Sugimoto, H.; Fujiwara, T. PCT Int. Appl. WO 96 10, 019, 1996, 396 pp; *Chem. Abstr.* **1996**, *125*, 114616k. (g) Adams, J. L.; Gallagher, T. F.; Sisko, J.; Peng, Z.-Q.; Osifo, I. K.; Boehm, J. C. PCT Int. Appl. WO 96 40, 143, 1996, 96 pp; *Chem. Abstr.* **1997**, *126*, 144274k. (h) Kawanami, E.; Okada, M.; Seki, N.; Naya, H.; Kudo, M. Jpn. Kokai Tokkyo Koho JP 09 71, 586, 1997; *Chem. Abstr.* **1997**, *127*, 5093h.

(35) (a) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc., Perkin Trans 1* **1981**, 1531. (b) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *Synthesis* **1980**, 133. (c) Meth-Cohn, O.; Rhouati, S.; Tarnowski, B. *J. Chem. Soc., Perkin Trans 1* **1981**, 1537.

Scheme 8



companied by chloroformylation at the carbonyl group to yield the iminium species **18** (Scheme 8). This iminium ion is readily transformed into its resonance structure **19** where the iminium nitrogen is on the aromatic ring. The [3 + 2] cycloaddition of the iminium ion **19** by the azide moiety is not possible, and therefore the reaction follows a different pathway. The intramolecular attack of the resultant iminium species by the azide proceeds and subsequent proton abstraction and elimination of nitrogen yields the corresponding imidazole-4-carboxaldehyde **15** on hydrolysis.

In conclusion, the azide group attached to the active methylene group of carbonyl compounds acts as a source for the generation of vinyl azides under Vilsmeier conditions. These vinyl azides could be cyclized in situ at higher temperatures by the intramolecular attack of the azide functionality by iminium species. Further studies are in progress to extend the scope of the reaction for the synthesis of more nitrogen heterocycles by replacing the carbonyl group with other active functional groups.

Experimental Section

Melting points were measured in capillary tubes and are uncorrected. Analytical thin-layer chromatography was performed on precoated sheets of silica gel with a 0.25 mm thickness containing PF_{254} indicator (Merck, Darmstadt). Column chromatography was performed with silica gel (60−120 mesh; SD fine, Boisar, India).

2-Azido-1-arylethanones. To an ice-cooled magnetically stirred solution of 2-bromo-1-arylethanone (1 equiv) in DMF was added 2 equiv of NaN_3 in one portion. The suspension was stirred for 10−30 min. The completion of the reaction was followed by TLC (20% EtAc in petroleum ether as eluant). The reaction mixture was poured onto crushed ice to yield the corresponding azides in good yield.

***N*-Substituted 2-Azidoacetamides.** NaN_3 (2 equiv) was added in one portion to a stirred solution of *N*-substituted 2-chloroacetamide in DMF. The suspension was stirred for 6−10 h at room temperature. The completion of the reaction was followed by TLC (30% EtAc in petroleum ether as eluant). The reaction mixture was poured onto crushed ice, and the solid product was filtered and dried to yield the corresponding azides in considerable yield.

2-Azido-*N*-(2-phenylethyl)acetamide and 2-azido-*N*-(phenylmethyl)acetamide were prepared by a slight modification in the workup. After pouring onto crushed ice, these azides were extracted with CH_2Cl_2 and dried (Na_2SO_4), and the solvent was evaporated in a vacuum.

2-Bromo-1-arylethanones.[36] These compounds were conveniently prepared by the dropwise addition of liquid bromine at 0−5 °C to a mechanically stirred solution of the corresponding acetophenone in ether or glacial acetic acid in the presence of catalytic amount of anhyd $AlCl_3$.

Typical Experimental Procedure for the Synthesis of Oxazole-4-carboxaldehydes (3a−d). Method A. A solution of 1-aryl-2-azidoethanone (5 mmol) in DMF (2 mL) was added dropwise to an ice-cooled magnetically stirred mixture of Vilsmeier reagent prepared from DMF (3 equiv) and $POCl_3$ (3 equiv). The reaction mixture was gradually allowed to attain room temperature and maintained at 80−90 °C for 3 h. The residual solution was poured into crushed ice, stirred for 1 h, extracted with $CHCl_3$ (3 × 50 mL), concentrated, and column chromatographed (petroleum ether: EtAc) to yield the oxazolecarboxaldehydes in moderate yields.

Method B. NaN_3 (1.1 equiv) was added in one portion to an ice-cooled, stirred solution of 1-aryl-2-bromoethanone (10 mmol) in DMF (10 mL). After stirring the suspension for 10−20 min, 3 equiv of $POCl_3$ was added dropwise. The temperature was gradually allowed to attain 80−90 °C and maintained at this temperature for 4−6 h. The crude product was worked up as in method A.

5-(4-Methylphenyl)oxazole-4-carboxaldehyde (3a). Prepared by following method A from 2-azido-1-(4-methylphenyl)-ethanone (**1a**, 0.88 g, 5 mmol). The crude product was purified by chromatography (10% EtAc in petroleum ether as eluant) to afford pure **3a** (0.34 g, 1.82 mmol) as colorless needles in 36% yield.

Prepared from 2-bromo-1-(4-methylphenyl)ethanone (**2a**, 2.13 g, 10 mmol) following method B. The crude product was chromatographed (10% EtAc in petroleum ether) to afford pure **3a** (0.84 g, 4.51 mmol) as colorless needles in 45% yield: mp 90 °C; R_f (25% ethyl acetate/petroleum ether) = 0.75; MS *m/e* 187 (M^+);^{1}H NMR (300 MHz) δ 9.97 (s, 1H), 8.27 (s, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz) δ 184.08, 163.24, 144.26, 142.00, 130.15, 129.57, 126.87, 123.35, 21.56. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.85; H, 4.87; N, 7.53.

5-(4-Chlorophenyl)oxazole-4-carboxaldehyde (3b). Prepared from 2-azido-1-(4-chlorophenyl)ethanone (**1b**, 0.98 g, 5 mmol) following the method A. The crude product was chromatographed (10% EtAc in petroleum ether) to afford pure **3b** (0.84 g, 4.51 mmol) as colorless solid in 36% yield.

Prepared from 2-bromo-1-(4-chlorophenyl)ethanone (**2b**, 2.34 g, 10 mmol) following method B. The crude product was chromatographed (10% EtAc in petroleum ether) to afford pure **3b** (0.84 g, 4.51 mmol) as colorless solid in 48% yield: mp 130 °C; R_f (25% ethyl acetate/petroleum ether) = 0.74; GCMS *m/e* (rel intensity) 209 (M + 2, 28), 207 (M^+, 85), 179 (24), 140 (33), 138 (100), 137 (26), 124 (24), 123 (20), 89 (50), 75 (23); ^{1}H NMR (300 MHz) δ 9.98 (s, 1H), 8.31 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz) δ 183.60, 162.31, 144.20, 141.55, 137.48, 129.04, 127.90, 124.26; IR (KBr) 2842, 1696, 1118, 796, 733 cm^{-1}. Anal. Calcd for $C_{10}H_6ClNO_2$: C, 57.85; H, 2.91; N, 6.75. Found: C, 58.08; H, 2.94; N, 6.78.

5-(4-Bromophenyl)oxazole-4-carboxaldehyde (3c). Prepared from 2-azido-1-(4-bromophenyl)ethanone (**1c**, 1.2 g, 5 mmol) following method A. The crude product was chromatographed (10% EtAc in petroleum ether) to afford pure **3c** (0.53 g, 2.09 mmol) as colorless solid in 42% yield.

Prepared from 2-bromo-1-(4-bromophenyl)ethanone (**2c**, 2.78 g, 10 mmol) following method B. The crude product was chromatographed (10% EtAc in petroleum ether) to afford pure **3c** (1.42 g, 5.63 mmol) as colorless solid in 56% yield: mp 135 °C; R_f (25% ethyl acetate/petroleum ether) = 0.78; GCMS *m/e* (rel intensity) 253 (M + 2, 93), 251 (M^+, 95), 223 (28), 200 (68),

(36) (a) *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Longman: UK, 1978; p 815. (b) Cowper, R. M.; Davidson, L. H. *Organic Syntheses*; Wiley: New York, 1943; Coll. Vol. II., p 480.

183 (88), 182 (86), 157 (33), 155 (34), 126 (18), 116 (38), 102 (24), 89 (88); ^{1}H NMR (300 MHz) δ 9.64 (s, 1H), 8.22 (s, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz) δ 183.38, 161.83, 146.11, 141.86, 131.94, 131.19, 131.02, 128.10; IR (KBr) 2873, 1689, 1398, 804 cm^{-1}. Anal. Calcd for $C_{10}H_6BrNO_2$: C, 47.65; H, 2.40; N, 5.56. Found: C, 47.40; H, 2.39; N, 5.58.

5-[(1,1′-Biphenyl)-4-yl]oxazole-4-carboxaldehyde (3d). Prepared from 2-azido-1-[(1,1′-biphenyl)-4-yl]ethanone (**1d**, 1.19 g, 5 mmol) following method A. The crude product was chromatographed (15% EtAc in petroleum ether) to afford pure **3d** (0.56 g, 2.24 mmol) as colorless solid in 45% yield.

Prepared from 1-[(1,1′-biphenyl)-4-yl]-2-bromoethanone (**2d**, 2.75 g, 10 mmol) following method B. The crude product was chromatographed (15% EtAc in petroleum ether) to afford pure **3d** (1.51 g, 6.06 mmol) as colorless solid in 61% yield: mp 160 °C; R_f (25% ethyl acetate/petroleum ether) = 0.77; MS *m/e* 249 (M$^+$); ^{1}H NMR (300 MHz) δ 9.61 (s, 1H), 8.21 (s, 1H), 7.78 (d, J = 7.8 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.09−6.99 (m, 5H); ^{13}C NMR (75 MHz) 183.54, 167.72, 144.83, 143.56, 129.91, 128.62, 127.78, 127.14, 127.09, 126.82, 126.69, 126.51; IR (KBr) 2923, 2834, 1681, 1316, 746 cm^{-1}. Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 76.80; H, 4.46; N, 5.59.

Typical Experimental Procedure for the Synthesis of α-Azido-*β*-chlorovinyl Azides (8a−e). A solution of 1-aryl-2-azidoethanone (5 mmol) in DMF (5 mL) was added dropwise to an ice-cooled magnetically stirred mixture of Vilsmeier reagent prepared from DMF (5 mL) and $POCl_3$ (3 equiv). The reaction mixture was gradually allowed to attain room temperature and maintained at this temperature for 6 h. The residue was then poured into crushed ice, stirred for 1 h, filtered, dried, and column chromatographed to yield α-azido-*β*-chlorovinyl azides in necessary yield.

2-Azido-3-chloro-3-(4-methylphenyl)-2-propenal (8a). The general procedure was followed by use of 2-azido-1-(4-methylphenyl)ethanone (**1a**, 0.88 g, 5 mmol). The crude product was purified by passing through a column of silica gel using petroleum ether as eluant. Recrystallization from petroleum ether gave colorless crystals of **8a** (0.77 g, 3.48 mmol) in 70% yield: mp 70 °C; R_f (10% ethyl acetate/petroleum ether) = 0.86; MS *m/e* 193 (M − 28); ^{1}H NMR (300 MHz) δ 9.39 (s, 1H), 7.32−7.23 (several peaks, 4H), 2.39 (s, 3H); ^{13}C NMR (75 MHz) δ 184.44, 141.74, 141.03, 134.12, 130.78, 130.41, 129.39, 21.38; IR (KBr) 2895, 2861, 2107, 1669, 1338, 813, cm^{-1}. Anal. Calcd for $C_{10}H_8ClN_3O$: C, 54.19; H, 3.64; N, 18.96. Found: C, 54.36; H, 3.66; N, 19.03.

2-Azido-3-chloro-3-(4-chlorophenyl)-2-propenal (8b). The general procedure was followed by use of 2-azido-1-(4-chlorophenyl)ethanone (**1b**, 0.98 g, 5 mmol). The crude product was purified by passing through a column of silica gel using petroleum ether as eluant. Recrystallization from petroleum ether gave colorless crystals of **8b** (0.75 g, 3.09 mmol) in 62% yield: mp 98 °C; R_f (10% ethyl acetate/petroleum ether) = 0.91; GCMS *m/e* (rel intensity) 215([(M + 2) − 28], 65), 213([M − 28], 100), 185 (31), 158 (28), 150 (56), 138 (46), 123 (46), 113 (39), 111 (92), 75 (87); ^{1}H NMR (300 MHz) δ 9.38 (s, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz) δ 183.85, 138.73, 137.44, 135.10, 132.10, 131.62, 129.09; IR (KBr) 2930, 2842, 2108, 1669, 1333, 1094, 816 cm^{-1}. Anal. Calcd for $C_9H_5Cl_2N_3O$: C, 44.66; H, 2.08; N, 17.36. Found: C, 44.83; H, 2.09; N, 17.47.

2-Azido-3-(4-bromophenyl)-3-chloro-2-propenal (8c). The general procedure was followed by use of 2-azido-1-(4-bromophenyl)ethanone (**1c**, 1.2 g, 5 mmol). The crude product was purified by chromatography (5% EtAc in petroleum ether as eluant). Recrystallization from petroleum ether gave colorless crystals of **8c** (0.94 g, 3.27 mmol) in 65% yield: mp 104 °C; R_f (10% ethyl acetate/petroleum ether) = 0.87; MS *m/e* 257 (M − 28); ^{1}H NMR (300 MHz) δ 9.38 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz) δ 183.83, 138.53, 134.82, 132.54, 132.06, 131.79, 122.27. Anal. Calcd for $C_9H_5BrClN_3O$: C, 37.73; H, 1.76; N, 14.67. Found: C, 37.89; H, 1.79; N, 14.89.

2-Azido-3-[(1,1′-biphenyl)-4-yl]-3-chloro-2-propenal (8d). The general procedure was followed by use of 2-azido-1-[(1,1′-biphenyl)-4-yl]ethanone (**1d**, 1.19 g, 5 mmol). The crude product was purified by chromatography (5% EtAc in petroleum ether as eluant) to give colorless crystals of **8d** (1.13 g, 3.98 mmol) in 80% yield: mp 103 °C; R_f (10% ethyl acetate/petroleum ether) = 0.86; MS *m/e* 255 (M − 28); ^{1}H NMR (300 MHz) δ 9.48 (s, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.61−7.40 (several peaks, 7H); ^{13}C NMR (75 MHz) δ 184.31, 143.95, 139.32, 134.74, 132.61, 130.98, 129.02, 128.29, 127.29, 127.11. IR (KBr) 2903, 2862, 2106, 1679, 1334, 810, 767 cm^{-1}. Anal. Calcd for $C_{15}H_{10}ClN_3O$: C, 63.50; H, 3.55; N, 14.81. Found: C, 63.79; H, 3.61; N, 15.03.

2-Azido-3-chloro-3-(3-methylphenyl)-2-propenal (8e). The general procedure was followed by use of 2-azido-1-(3-methylphenyl)ethanone (**1e**, 1.75 g, 10 mmol). The crude product was purified by passing through a column of silica gel using 2% EtAc in petroleum ether as eluant. Recrystallization from petroleum ether gave colorless crystals of **8e** (1.42 g, 6.43 mmol) in 64% yield: mp 95 °C; MS *m/e* 193 (M − 28); ^{1}H NMR (300 MHz) δ 9.40 (s, 1H), 7.31−7.23 (several peaks, 4H), 2.38 (s, 3H); ^{13}C NMR (75 MHz) δ 184.38, 140.66, 138.61, 134.45, 133.47, 131.74, 130.84, 128.44, 127.55, 21.14; IR (KBr) 2922, 2892, 2102, 1663, 1333, 835, 799 cm^{-1}. Anal. Calcd for $C_{10}H_8ClN_3O$: C, 54.19; H, 3.64; N, 18.96. Found: C, 54.25; H, 3.65; N, 18.99.

Typical Experimental Procedure for the Synthesis of N-Substituted 5-Chloro-2-(dimethylamino)imidazole-4-carboxaldehydes (15a−h). N-Substituted 2-azidoacetamide (10 mmol) was dissolved in DMF (5 mL) and cooled to 0−5 °C. To the stirred solution was added $POCl_3$ (30 mmol, 2.5 mL) dropwise, and the temperature was gradually allowed to attain 80−90 °C and maintained at this temperature for 5 h. The reaction mixture was then poured cautiously into water (40 mL), stirred for 1 h, extracted with dichloromethane (3 × 50 mL), dried (Na_2SO_4), and concentrated. The crude product was column chromatographed (petroleum ether: EtAc) to yield the imidazolecarboxaldehydes in varying yields.

5-Chloro-2-(dimethylamino)-1-phenyl-1*H*-imidazole-4-carboxaldehyde (15a). The general procedure was followed by use of 2-azido-*N*-phenylacetamide (**12a**, 1.75 g, 10 mmol), DMF (5 mL, 65 mmol), and $POCl_3$ (2.5 mL, 27 mmol). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtAc in petroleum ether as eluant) to give pure **15a** (1.12 g, 4.49 mmol) as a pale yellow solid in 45% yield: mp 93 °C; R_f (40% ethyl acetate/petroleum ether) = 0.54; MS *m/e* 249 (M$^+$); ^{1}H NMR (300 MHz) δ 9.65 (s, 1H), 7.40−7.38 (m, 3H), 7.20 (d, J = 6.3 Hz, 2H), 2.51 (s, 6H); ^{13}C NMR (75 MHz) 182.15, 153.42, 135.68, 132.54, 132.28, 130.06, 128.70, 124.91, 40.89. IR (KBr) 3044, 2818, 1675, 1576, 1400, 825, 702 cm^{-1}. Anal. Calcd for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.84; N, 16.83. Found: C, 57.97; H, 4.87; N, 16.89.

5-Chloro-1-(4-chlorophenyl)-2-(dimethylamino)-1*H*-imidazole-4-carboxaldehyde (15b). Prepared by following the general procedure from 2-azido-*N*-(4-chlorophenyl)acetamide (**12b**, 2.10 g, 10 mmol). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtAc in petroleum ether as eluant) to give pure **15b** (1.36 g, 4.78 mmol) as a pale yellow solid in 48% yield: mp 100 °C; R_f (40% ethyl acetate/petroleum ether) = 0.57; MS *m/e* 279 (M$^+$); ^{1}H NMR (300 MHz) δ 9.78 (s, 1H), 7.48 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 7.2 Hz, 2H), 2.63 (s, 6H); ^{13}C NMR (75 MHz) 182.12, 153.32, 135.65, 132.51, 132.25, 130.02, 128.67, 124.82, 40.86. IR (KBr) 2881, 2835, 1677, 1590, 1247, 849, 821 cm^{-1}. Anal. Calcd for $C_{12}H_{11}Cl_2N_3O$: C, 50.72; H, 3.90; N, 14.79. Found: C, 50.89; H, 3.92; N, 14.83.

5-Chloro-2-(dimethylamino)-1-(4-methoxyphenyl)-1*H*-imidazole-4-carboxaldehyde (15c). Prepared by following the general procedure from 2-azido-*N*-(4-methoxyphenyl)-acetamide (**12c**, 2.05 g, 10 mmol). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtAc in petroleum ether as eluant) to give pure **15c** (1.62 g, 5.79 mmol) as a pale yellow solid in 58% yield: mp 108 °C; R_f (40% ethyl acetate/petroleum ether) = 0.43; MS *m/e* 277 (M$^+$); ^{1}H NMR (300 MHz) δ 9.72 (s, 1H), 7.17 (d, J = 8.1 Hz,

2H), 6.95 (d, J = 8.1 Hz, 2H), 3.79 (s, 3H), 2.58 (s, 6H); ^{13}C NMR (75 MHz) 182.18, 160.15, 153.59, 131.92, 129.35, 127.88, 125.74, 114.04, 54.76, 40.12. Anal. Calcd for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.04; N, 15.02. Found: C, 56.04, H, 5.08; N, 15.13.

5-Chloro-1-(3-chlorophenyl)-2-(dimethylamino)-1*H*-imidazole-4-carboxaldehyde (15d). Prepared by following the general procedure from 2-azido-*N*-(3-chlorophenyl)acetamide (**12d**, 2.10 g, 10 mmol). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtAc in petroleum ether as eluant) to give pure **15d** (1.10 g, 3.87 mmol) as a pale yellow solid in 39% yield: mp 119 °C; R_f (40% ethyl acetate/petroleum ether) = 0.55; MS *m/e* 283 (M^+); ^{1}H NMR (300 MHz) δ 9.78 (s, 1H), 7.24 (s, 1H), 7.33 (s, 1H), 7.46 (m, 2H), 2.62 (s, 6H); ^{13}C NMR (75 MHz) 182.21, 153.30, 135.39, 135.17, 132.36, 130.77, 129.96, 127.63, 125.75, 124.71, 40.92. IR (KBr) 2878, 2850, 1684, 1577, 833 cm^{-1}. Anal. Calcd for $C_{12}H_{11}Cl_2N_3O$: C, 50.72; H, 3.90; N, 14.79. Found: C, 50.51; H, 3.92; N, 14.80.

5-Chloro-2-(dimethylamino)-1-(4-methylphenyl)-1*H*-imidazole-4-carboxaldehyde (15e). Prepared by following the general procedure from 2-azido-*N*-(4-methylphenyl)acetamide (**12e**, 1.89 g, 10 mmol). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtAc in petroleum ether as eluant) to give pure **15e** (1.62 g, 6.15 mmol) as a pale yellow solid in 62% yield: mp 123 °C; R_f (40% ethyl acetate/petroleum ether) = 0.57; GCMS *m/e* (rel intensity) 265 (M + 2, 16), 263 (M^+, 52), 228 (88), 105 (28), 91 (31), 83 (100), 65 (21), 56 (18); ^{1}H NMR (300 MHz) δ 9.76 (s, 1H), 7.27 (d, J = 7.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 2H), 2.58 (s, 6H), 2.37 (s, 3H); ^{13}C NMR (75 MHz) 182.12, 153.51, 139.88, 132.06, 131.52, 130.34, 127.15, 125.43, 40.80, 21.20. Anal. Calcd for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; N, 15.93. Found: C, 59.41; H, 5.37; N, 16.00.

5-Chloro-2-(dimethylamino)-1-(2-ethylphenyl)-1*H*-imidazole-4-carboxaldehyde (15f). Prepared by following the general procedure from 2-azido-*N*-(2-ethylphenyl)acetamide (**12f**, 2.03 g, 10 mmol). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtAc in petroleum ether as eluant) to give pure **15f** (1.0 g, 3.60 mmol) as a viscous yellow liquid in 36% yield; R_f (40% ethyl acetate/petroleum ether) = 0.61; MS *m/e* 277 (M^+); ^{1}H NMR (300 MHz) δ 9.74 (s, 1H), 7.36−7.44 (several peaks, 2H), 7.28 (m, 1H), 7.13 (d, J = 7.2 Hz, 1H), 2.58 (s, 6H), 2.28 (q, J = 7.4 Hz, 2H), 1.04 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz) 181.88, 153.06, 141.76, 132.55, 131.99, 130.34, 129.49, 128.56, 126.94, 125.52, 40.52, 23.57, 13.36. IR (neat) 2876, 2810, 1686, 1569, 827, 762 cm^{-1}. Anal. Calcd for $C_{14}H_{16}ClN_3O$: C, 60.54; H, 5.81; N, 15.13. Found: C, 60.80; H, 5.83; N, 15.23.

5-Chloro-2-(dimethylamino)-1-(2-naphthyl)-1*H*-imidazole-4-carboxaldehyde (15 g). Prepared by following the general procedure from 2-azido-*N*-(2-naphthyl)acetamide (**12g**, 2.25 g, 10 mmol). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtAc in petroleum ether as eluant) to give pure **15g** (1.54 g, 5.14 mmol) as a pale yellow solid in 51% yield: mp 151 °C; R_f (40% ethyl acetate/petroleum ether) = 0.56; GCMS *m/e* (rel intensity) 301 (M + 2, 14), 299 (M^+, 41), 264 (75), 141 (23), 127 (47), 111 (15), 83 (100), 56 (28), 42 (41); ^{1}H NMR (300 MHz) δ 9.78 (s, 1H), 7.91−7.76 (several peaks, 4H), 7.53 (m, 2H), 7.34 (s, 1H), 2.58 (s, 6H); ^{13}C NMR (75 MHz) 182.21, 153.62, 133.04, 132.25, 131.46, 129.93, 128.20, 127.91, 127.68, 127.34, 126.58, 125.46, 124.43, 40.88. IR (KBr) 2822, 1674, 1583, 1258, 817, 752 cm^{-1}. Anal. Calcd for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02. Found: C, 64.37; H, 4.78; N, 14.23.

5-Chloro-2-(dimethylamino)-1-(2-methylphenyl)-1*H*-imidazole-4-carboxaldehyde (15h). Prepared by following the general procedure from 2-azido-*N*-(2-methylphenyl)acetamide (**12h**, 1.89 g, 10 mmol). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtAc in petroleum ether as eluant) to give pure **15h** (1.07 g, 4.06 mmol) as a pale yellow solid in 41% yield: mp 79 °C; R_f (40% ethyl acetate/petroleum ether) = 0.57; MS *m/e* 263 (M^+); ^{1}H NMR (300 MHz) δ 9.79 (s, 1H), 7.42−7.31 (several peaks, 3H), 7.17 (m, 1H), 2.62 (s, 6H), 2.05 (s, 3H); ^{13}C NMR (75 MHz) 182.14, 153.18, 136.34, 133.40, 132.27, 131.48, 130.25, 128.55, 127.27, 125.38, 40.62, 17.43. IR (KBr) 3048, 2839, 2769, 1687, 1564, 825, 768 cm^{-1}. Anal. Calcd for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; N, 15.93. Found: C, 59.08; H, 5.37; N, 15.99.

5-Chloro-2-(dimethylamino)-1-(phenylmethyl)-1*H*-imidazole-4-carboxaldehyde (17a). Prepared by following the general procedure from 2-azido-*N*-(phenylmethyl)acetamide (**16a**, 1.89 g, 10 mmol). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtAc in petroleum ether as eluant) to give pure **17a** (0.28 g, 0.11 mmol) as a pale yellow solid in 11% yield: mp 93 °C; R_f (40% ethyl acetate/petroleum ether) = 0.53; MS *m/e* 263 (M^+); ^{1}H NMR (300 MHz) δ 9.80 (s, 1H), 7.31 (d, J = 6.4 Hz, 2H), 7.25 (s, 1H), 7.08 (d, J = 6.3 Hz, 2H), 5.11 (s, 2H), 2.71 (s, 6H); ^{13}C NMR (75 MHz) 182.41, 154.30, 134.83, 132.42, 128.99, 128.01, 126.07, 47.14, 42.75. IR (KBr) 2855, 2809, 1677, 1565, 848, 749 cm^{-1}. Anal. Calcd for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; N, 15.93. Found: C, 59.46; H, 5.36; N, 16.04.

5-Chloro-2-(dimethylamino)-1-(2-phenylethyl)-1*H*-imidazole-4-carboxaldehyde (17b). Prepared by following the general procedure from 2-azido-*N*-(2-phenylethyl)acetamide (**16b**, 2.03 g, 10 mmol). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtAc in petroleum ether as eluant) to give pure **17b** (0.56 g, 2.03 mmol) as a pale yellow solid in 20% yield: mp 55 °C; R_f (40% ethyl acetate/petroleum ether) = 0.51; MS *m/e* 277 (M^+); ^{1}H NMR (300 MHz) δ 9.68 (s, 1H), 7.21−7.14 (several peaks, 3H), 7.00 (d, J = 6.7 Hz, 2H), 4.04 (dd, J = 7.8, 6.8 Hz, 2H), 2.96 (dd, J = 7.7, 6.8 Hz, 2H), 2.64 (s, 6H); ^{13}C NMR (75 MHz) 182. 11, 153.89, 136.46, 132.07, 130.73, 128.56, 126.89, 125. 21, 124.15, 45.17, 42.48, 34.98. Anal. Calcd for $C_{14}H_{16}ClN_3O$: C, 60.54; H, 5.81; N, 15.13. Found: C, 60.81; H, 5.85; N, 5.21.

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Supporting Information Available: Copies of NMR spectra (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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