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The stereoselective synthesis of highly functionalized tertiary 3-aminoindoles/anilines or dihydropyrroles from *C*-(3-indolyl)-*N*-aryl and *C*,*N*-diaryl nitrones

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ABSTRACT

We report on the novel properties of nitrones including their transformations via reactions with sodium malonates to give functionalized stereodefined derivatives of tertiary 3-aminoindoles or anilines, as well as fully-substituted dihydropyrroles. The outcome of the reactions is dependent mainly upon the nature of the starting *C*-nitrone substituent and solvent used. The formation of a new carbon–nitrogen bond in the obtained amines occurs via a nucleophilic 1,2-aryl/3-indolyl shift from C to the adjacent nitrogen.

Among the wide variety of privileged indole scaffold structures, the novel 3-aminoindole core only appeared recently. 3-Aminondole derivatives, though not easily accessible, have nevertheless emerged as promising agents with potential application in the design of drugs against a large number of diseases.[1] 3-Aminoindole-based compounds are commonly prepared from the corresponding 3-substituted indoles,[1a,b,2] indoxyls,[1c,3] and non-indolic precursors.[1d–f,4] New, facile, and efficient syntheses of 3-amino-2-phenylindoles were effected by direct cyclization of 2-(disubstituted amino)benzonitriles in the presence of a base.[5] Among other base-catalyzed methods for the synthesis of 2-substituted 3-alkyl/arylaminoindoles, one can mention the interrupted Ugi reaction.[6] However, all these methods appear limited in both the degree and type of functionality at the amino group and the indole nucleus.

As a part of our continuing interest in the synthesis of bioactive indole scaffolds, we have developed an efficient method for both diversification of the 3-aminoindole structure by forming a new carbon–nitrogen bond and the synthesis of their aromatic analogs. In previous work, we reported the preparation of functionalized tertiary 3-aminoindoles tethered to a methylidene malonate acid fragment as mixtures of *Z*:*E* isomers (methylidene malonate series) in benzene, from easily available indole-3-carbaldehyde based nitrones and sodium malonate.[7] An important application of these 3-aminoindole derivatives with a free position at C-2 was their conversion into potential antituberculosis δ-carbolines.[8] A typical feature of the former reaction is the 1,2-(3-indolyl) shift from carbon to the nitrogen atom. However, the reported rearrangement was not general for all nitrones and was relevant to a few *C*-(3-indolyl)-*N*-aryl nitrones only. It is well known that nitrones generally react with sodium malonates and other C-nucleophiles affording hydroxylamines,[9] 3,4-disubstituted isoxazolidin-5-ones,[10] alkenes,[11] and aziridines.[12] The reaction of *C*,*N*-diaryl nitrones with sodium malonates has not been investigated so far. In the present work, we report that the reaction of other nitrones with sodium malonates results in the formation of new products, some of them possessing unexpected fully-substituted dihydropyrrole structures as well as stereodefined derivatives of tertiary 3-aminoindoles and anilines.

To further delineate the factors governing the chemoselectivity of the reactions between nitrones and sodium malonate, we investigated the reactions of *C*-(3-indolyl)-*N*-aryl and *C*,*N*-diaryl nitrones **1a**–**g** and **2a**–**k** of various nucleophilicity. The reactions of *C*-(3-indolyl)-*N*-phenyl and *C*,*N*-diphenyl nitrones **1a** and **2a** with dimethyl sodium malonate **3a** (R^4 = Me) in refluxing nonpolar benzene or toluene afforded the corresponding acid from the methylidene malonate series as a mixture of *Z*,*E*-isomers, but in moderate yield, and as complex non-separable mixtures of compounds. On the other hand, replacing benzene with alcoholic solvents altered the reaction path. Direct conversion of *C*-(3-indolyl) nitrone **1a** into the sodium salt **4a** (88%) was achieved in the presence of a twofold excess of **3a** after a short period of reflux in methanol (Scheme 1). The ^{1}H and ^{13}C NMR spectra of **4a** revealed one set of signals, indicating that one geometric isomer was obtained. The latter was characterized by 1D and 2D NMR spectroscopic methods and mass spectrometry as the rearranged tertiary 3-aminoindole derivative of *Z*-configuration. In the ^{1}H NMR spectrum the signal for the N–CH= proton was observed as a singlet at 7.81 ppm. The close spatial orientation of the indole nucleus to the alkoxy ester protons in **4a** (pointing to the *Z*-configuration of the double bond) was proved by NOESY experiments.

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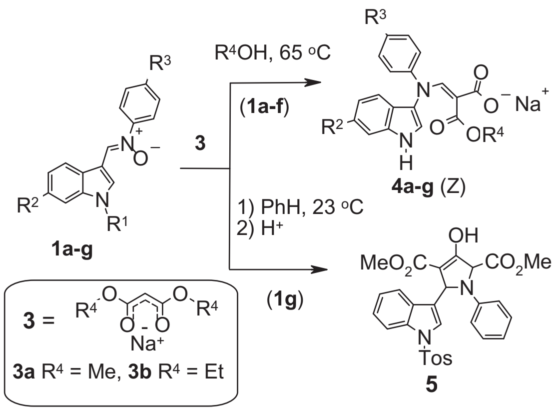
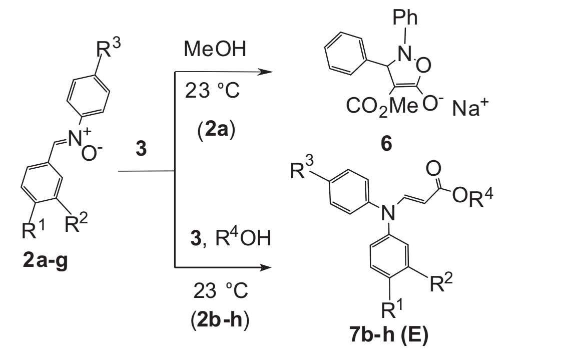


Scheme 1. The synthesis of 3-aminoindole derivatives **4** and dihydropyrrole **5** from *C*-(3-indolyl)-*N*-aryl nitrones **1** and sodium malonates.



Scheme 2. The synthesis of ISOX salt **6** and diarylamine derivatives **7b**–**7h** from *C*,*N*-diarylnitrones **2b**–**2g** and sodium malonates **3**.

Besides, a signal due to a strongly shielded ester CH_3O group in **4a** was observed upfield at 2.55 ppm, compared to ca. 3.5 ppm as is commonly observed in methyl esters. Following the successful preparation of salt **4a**, the generality of this procedure was studied using nitrones with substituents of various nucleophilicity on the *C*-(3-indolyl) as well as the *C*- and *N*-aryl moieties.

Similarly, reactions of other *N*-aryl substituted indolyl nitrones **1b**–**f** (even examples containing moderately electron-poor aryl groups [R^3 = F, CO_2Et, CN] attached to the nitrogen atom of the nitrone functionality) and diethyl sodium malonate **3b** took the same course resulting in salts **4b**–**g** as single isomers in 54–97% yields (Scheme 1, Table 1). The ^{1}H and ^{13}C NMR spectra of salts **4b**–**g** closely resembled the spectrum of **4a**, thus, all the products have the *Z*-configuration. Hence, we have shown that in alcohols the C-to-N rearrangement occurs with high stereoselectivity to give (*Z*)-methylidene malonate salts **4**.

Surprisingly, introduction of an electron-withdrawing tosyl substituent on the indole nitrogen altered dramatically the course of the reaction. An unexpected compound, dihydropyrrole **5**, was isolated in <10% yield when nitrone **1g** was treated with sodium malonate in methanol. Formally, the unrearranged dihydropyrrole **5** was formed from one and two equivalents of **1g** and **3a**, respectively, with retention of the bonds of the nitrone functionality (Scheme 1). In benzene at rt a threefold excess of **3a** was required to increase the yield of **5** to 41%. Compound **5** exhibited characteristic chemical shifts of the N–CH groups in the ^{1}H and ^{13}C NMR spectra (4.50 and 5.70 ppm and 58.0 and 70.5 ppm, respectively).

Next, at 23 °C in methanol, the reaction of *C*,*N*-diphenyl nitrone **2a** with **3a** gave highly unstable 5-isoxazolidinone salt **6** (ISOX) in 71% yield (Scheme 2). In this case *C*,*N*-diphenyl nitrone **2a** behaved in exactly the same way as its *C*-aryl-*N*-methyl analogs under similar conditions.[10] The spectral characteristics of ISOX salt **6** correspond to those of known similar ISOX salts.[10]

However, nitrones **2b**–**g** with electron-donating *C*-aryl groups reacted with sodium malonate **3a** with loss of CO_2 to afford acrylates **7b**–**g** as shown in Scheme 2. In particular, acrylate **7b** was obtained in 90% yield under the same conditions, but from virtually equimolar amounts of starting nitrone **2b** (R^1 = 4-Me_2N, R^2 = H) and **3a**. The acrylate **7b** was characterized by 1D and 2D NMR spectroscopic methods and mass spectrometry as the rearranged tertiary aniline derivative of *E*-configuration. In the ^{1}H NMR spectrum the signals of the vinylic N–CH=CH protons were observed as doublets at 8.07 and 4.55 ppm, $^3J_{trans}$ ca. 13 Hz. The signal due to the methoxy group in the *E*-isomer of **7b** occurred downfield at 3.51 ppm, compared to the *Z*-isomer of salt **4a**. Acrylates **7c**–**g** were obtained in good to high yields under similar mild conditions from nitrones **2c**–**g** with C-electron-donating aromatic groups only (and various *N*-aromatic groups, Scheme 2, Table 2). Similar reaction was then carried out using diethyl sodium malonate **3b** in refluxing ethanol to give the corresponding acrylate **7h**.

We also discovered that no C-to-N rearrangement occurred in the reactions of *C*-aryl nitrones **2a**,**i**–**k** (R^1 = H, Cl, F) in methanol when the *C*-aryl group does not contain highly electron-donating substituents. Dihydropyrroles **8a**,**i**–**k**, aromatic analogs of the dihydropyrrole **5**, were obtained in trace amounts instead of the rearranged products. However, the yields of compounds **8a**,**i**–**k** were improved to 30–62% by running the reaction in the presence of a threefold excess of **3a** and with an increased concentration of the latter (Scheme 3). The best solvent for this multistep reaction was benzene. Further optimization of the reaction conditions is in progress. The aliphatic part of the ^{1}H and ^{13}C NMR spectra of dihydropyrroles **8** closely resemble the spectra of **5**. All the other

Table 1
Reaction of *C*-(3-indolyl)-*N*-aryl nitrones **1a**–**f** with sodium malonates in MeOH and EtOH[a]

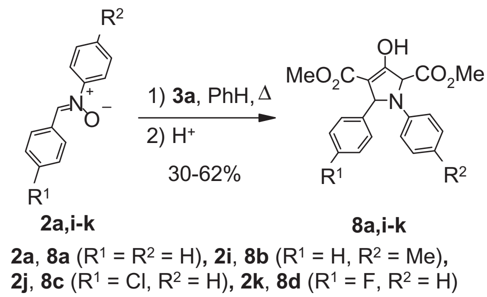
Substrate[b]	R^3	Product[c]	Yield[d] (%)
1a	H	**4a**	88
1a′	H	**4a′**	90
1b	CO_2Et	**4b**	87
1c	CN	**4c**	54
1d	F	**4d**	97[e]
1e	Me	**4e**	77
1f	Me	**4f**	78

[a] Conditions: nitrone (1 mmol), sodium malonate (2 equiv), 2–3 h.
[b] R^1 = H (**1a**–**f**, **4a**–**f**), R^2 = H (**1a**–**1d**, **1f**, **4a**–**d**, **4f**), R^2 = F (**1e**, **4e**).
[c] R^4 = Me (**4a**); R^4 = Et (**4a′**–**4f**).
[d] Isolated yield.
[e] 5% impure by ^{1}H NMR.

Table 2
The reaction of *C*,*N*-diarylnitrones **2b**–**g** with sodium malonates in MeOH and EtOH[a]

Substrate	R^1	R^2	R^3	Product[b]	Yield[c] (%)
2b	Me_2N	H	H	**7b**	90[d]
2c	Me_2N	H	Br	**7c**	83
2d	Me_2N	H	Me	**7d**	80
2e	OMe	H	H	**7e**	56
2f	OH	OMe	H	**7f**	55[e]
2g	OEt	OMe	H	**7g**	64
2b	Me_2N	H	H	**7h**	82

[a] Conditions: nitrone (1 mmol), sodium malonate (1.1 equiv), 23 °C, 1.5–3 h.
[b] R^4 = Me (**7b**–**g**), R^4 = Et (**7h**).
[c] Isolated yield.
[d] 1.5 equiv of methyl sodium malonate were used. Under standard conditions, the yield was 86% after 8 h.
[e] Low conversion obtained.



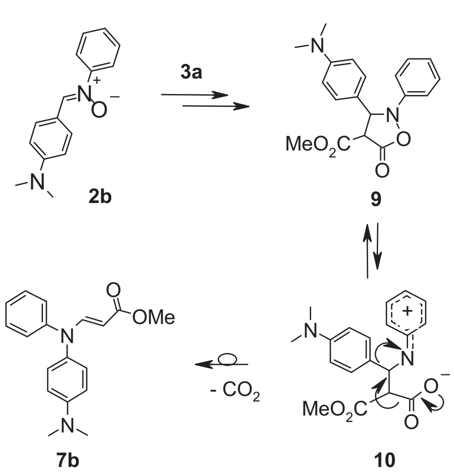
Scheme 3. The preparation of 2,5-dihydropyrroles from *C*,*N*-diarylnitrones **8a**,**i–k**.

signals in the prepared compounds were in agreement with the assigned structures. Finally, dihydropyrrole **8a** was oxidized into the corresponding pyrrole and the structure of the latter was confirmed employing X-ray analysis.[13]

These results revealed that the outcome of the reactions is dependent mainly upon the nature of the *C*-nitrone substituent, and to a certain extent, upon the nature of the solvent used. A new carbon–nitrogen bond is formed during the preparation of the corresponding tertiary amine derivatives as (*E*)-acrylates and (*Z*)-methylidene malonates from *C*-aryl and *C*-(3-indolyl) nitrones. The reactions occur in a stereoselective fashion but with different chemoselectivity. Thus, migration is favored for *C*-aryl/3-indolyl groups bearing electron-donating substituents, and this can be used to enable migration to a nitrogen cationic center as it occurs, for example, for the Stieglitz rearrangement of tritylamines.[14] It is evident that the formation of a new carbon–nitrogen bond in the obtained amines occurs via a nucleophilic 1,2-(3-indolyl)/aryl shift from C to the adjacent nitrogen.

Further evidence for the rearrangement was obtained from a cross-over experiment. The reaction of a mixture of **1b** and **1e** in methanol afforded two products, **4b** and **4e**, as determined by analysis of the ^{1}H and ^{19}F NMR and mass spectra of the reaction mixture. The fact that no cross-over products were observed indicated the intramolecular character of the rearrangement step.

The mechanism of these multistep reactions presumably involves initial formation of 3,4-disubstituted 5-isoxazolidinones, such as **9** (Scheme 4) and their salts similar to ISOX salt **6**. The latter can serve as key intermediates in the reactions depicted in Schemes 1–3. This is in line with the fact that the known reactions of the *C*-aryl-*N*-methyl[10] and *C*,*N*-diphenyl nitrone **2a** and sodium malonates result in the formation of substituted ISOX salts via a tandem Michael-type addition–intramolecular cyclization. Probably, the presence of an *N*-aryl substituent, compared to an *N*-methyl, facilitates cleavage of the relatively weak N–O bond in the ISOX salt to form *N*-aryl stabilized zwitterions, such as **10** (Scheme 4). A similar N-substitutent effect on N–O bond cleavage rates in isoxazolines was observed in the Brandi reaction.[15] Heterolytic N–O bond cleavage under mild conditions giving arylnitrenium ions with electron-withdrawing groups has been previously reported.[16]



Scheme 4. The proposed pathway for the formation of acrylate **7b**.

Scheme 4 outlines a probable reaction route for the formation of decarboxylated (*E*)-*N*,*N*-diaryl-substituted enaminoester **7b** from nitrone **2b** in polar methanol. It is likely that intermediate ISOX **9** undergoes a secondary reaction generating the open zwitterion **10**. The loss of CO_2 from **10** assists the aryl shift from the carbon to the adjacent nitrogen to furnish **7b** in a thermodynamically driven manner. The proton loss from ISOX **9** would lead to the formation of a non-decarboxylated product of type **4**. A similar isoxazolone rearrangement, under thermal conditions, was observed by Wentrup et al.[17] to involve cleavage of the N–O bond followed by loss of CO_2 and 1,2-migration of the phenyl group in the putative vinylnitrene.

In conclusion, highly functionalised tertiary 3-aminoindoles/anilines have been synthesized simply and stereoselectively from readily available nitrones and sodium malonates in high yields.[18,19] This stereoselective transformation is highly useful for further elaboration of stereodefined 3-aminoindole derivatives and a direct synthesis of functionalized δ-carbolines. Although the yields of the fully-substituted dihydropyrroles obtained are moderate,[20,21] it should be noted that the products can be used as novel scaffolds in the search for pharmacologically interesting pyrroles.

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18. *General procedure for the synthesis of sodium (2Z)-3-[(1H-indol-3-yl)(aryl)amino]-2-(alkoxycarbonyl)acrylates* **4a**–**g**. Alkyl malonate (2 mmol) was added to a freshly prepared sodium alkoxide solution [from 0.048 g (2 mmol) of Na and 7 mL of the corresponding anhydrous alcohol] and the mixture was stirred for 5 min at rt. *C*-[1*H*-(Indol-3-yl)]-*N*-aryl nitrone **1a**–**f** (1 mmol) was added in one portion and the reaction mixture was heated at 65 °C for 2 h. TLC analysis (1:1 v/v $CHCl_3$/AcMe) indicated complete consumption of the starting nitrone. The solvent was evaporated and Et_2O (10 mL) was added to the oily residue. The precipitate formed was filtered and recrystallized from aqueous EtOH. *Data for sodium (2Z)-3-[N-(1H-indol-3-yl)(phenyl)amino]-2-(methoxycarbonyl)acrylate* (**4a**): mp 197–200 °C. ^{1}H NMR (600 MHz, DMSO-d_6): 2.54 (s, 3H), 6.86–6.93 (m, 3H), 6.93–6.99 (m, 2H), 7.07 (ψt, *J* = 7.55 Hz, 1H, IndH-6) (ψt is pseudotriplet), 7.20–7.27 (m, 3H), 7.39 (d, *J* = 8.24 Hz, 1H, IndH-7), 7.8 (s, 1H), 11.36 (br s, 1H, IndH-1); ^{13}C NMR (125 MHz, DMSO-d_6): 169.37, 168.73, 142.28, 139.67, 135.34, 129.43, 124.13, 124.00, 122.35, 122.22, 121.81, 119.47, 118.57, 118.47, 118.31, 117.54, 112.73, 112.27, 49.79. ν_{max}(KBr)/cm^{-1}: 3383, 1694, 1677, 1614; ESI MS: [M+H]$^+$: 359.1012, calcd 359.1008 for $C_{19}H_{16}N_2NaO_4$.
19. *General procedure for the synthesis of alkyl (2E)-3-(diarylamino)acrylates* **7b**–**h**: alkyl malonate (1.15 mmol) was added to a freshly prepared sodium alkoxide solution [from 0.025 g (1.1 mmol) of Na and 3 mL of the corresponding anhydrous alcohol] and the mixture was stirred for 5 min at rt. *C*-Aryl-*N*-aryl nitrone **2** (0.271 g, 1 mmol) was added in one portion and the reaction mixture was stirred for the indicated time at rt. TLC analysis (10:1 v/v $CHCl_3$/AcMe) indicated complete consumption of the starting nitrone. The reaction mixture was cooled to 0 °C and cold H_2O (3 mL) was slowly added. The precipitate formed was filtered and washed with a mixture of CH_3OH and H_2O (1:1 v/v). *Data for methyl (2E)-3-[(4-ethoxy-3-methoxyphenyl)(phenyl) amino]acrylate* (**7g**): mp 121–122 °C. (0.21 g, 64%). ^{1}H NMR (300 MHz, DMSO-d_6): 1.33 (t, *J* = 6.8 Hz, 3H), 3.55 (s, 3H), 3.71 (s, 3H), 4.04 (q, *J* = 6.97 Hz, 2H), 4.54 (d, *J* = 12.89 Hz, 1H), 6.71 (dd, *J* = 2.44, 8.71 Hz, 1H), 6.8 (d, *J* = 2.44 Hz, 1H), 7.0–7.12 (m, 3H), 7.16 (ψt, *J* = 7.32 Hz, 1H), 7.33 (ψt, *J* = 7.84 Hz, 2H), 8.04 (d, *J* = 13.24 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 168.5, 147.7, 147.5, 135.2, 130.1, 124.9, 121.3, 118.8, 113.9, 110.5, 93.0, 64.3, 56.1, 50.9, 15.2. ν_{max}(KBr)/cm^{-1}: 2985, 1692, 1622, 1247. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.57; H, 6.49; N, 4.44.
20. *Synthesis of dimethyl 3-hydroxy-5-{1-[(4-methylphenyl) sulfonyl]-1H-indol-3-yl}-1-phenyl-2,5-dihydro-1H-pyrrole-2,4-dicarboxylate* **5**: benzene (2.5 mL) was added to NaOMe powder (0.113 g, 2.1 mmol), followed by methyl malonate (0.24 mL, 2.1 mmol) and the resulting mixture was stirred for 30 min at rt. *C*-{1-[(4-Methylphenyl)sulfonyl]-1*H*-indol-3-yl}-*N*-phenylnitrone (**1g**) (0.25 g, 0.7 mmol) was added in one portion and the reaction mixture was stirred for 4 h at rt. TLC analysis (10:1 v/v $CHCl_3$/AcMe) indicated complete consumption of the starting nitrone. The precipitated product was filtered. C_6H_6 was evaporated and Et_2O (5 mL) was added to the residue. The precipitate was filtered and the combined precipitates were washed repeatedly with boiling *i*PrOH and then with boiling EtOH. The obtained solid was stirred with 5% aqueous phosphoric acid and the precipitate was filtered and washed with H_2O. White solid, mp 150–152 °C. (0.155 g, 40%). For the major isomer: ^{1}H NMR (300 MHz, DMSO-d_6): 2.29 (s, 3H), 3.22 (s, 3H), 3.84 (s, 3H), 4.5 (s, 1H), 5.l7 (s, 1H), 6.26 (d, *J* = 8 Hz, 2H), 6.6 (ψt, *J* = 7.9 Hz, 1H), 7.02 (ψt, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.25–7.35 (m, 2H), 7.5 (d, *J* = 7.8 Hz, 2H), 7.8–7.9 (m, 1H), 7.95–8.1 (m, 1H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 174.5, 171.2, 147.2, 146.8, 146.1, 135.7, 134.7, 132.4, 131.0, 129.8, 126.3, 123.1, 122.7, 120.8, 115.3, 112.4, 111.7, 110.1, 90.7, 70.5, 58.0, 55.6, 51.2, 24.6. ν_{max}(KBr)/cm^{-1}: 1740, 1662; ESI MS: [M+H]$^+$: 547.1536, calcd 547.1533 for $C_{29}H_{27}N_2O_7S$. Anal. Calcd for $C_{29}H_{26}N_2O_7S{\cdot}H_2O$: C, 61.69; H, 5.00; N, 4.96. Found: C, 61.24; H, 4.67; N, 4.92.
21. *Synthesis of dimethyl 3-hydroxy-1,5-diphenyl-2,5-dihydro-1H-pyrrole-2,4-dicarboxylate* **8a**: benzene (3.4 mL) was added to NaOMe powder (0.384 g, 7.11 mmol), followed by methyl malonate (0.81 mL, 7.11 mmol) and the mixture was stirred for 30 min at rt. *C*,*N*-Diphenylnitrone **2a** (0.466 g, 2.37 mmol) was added in one portion and the reaction was refluxed for 0.5 h at rt. TLC analysis (10:1 v/v $CHCl_3$/AcMe) indicated complete consumption of the starting nitrone. The reaction mixture was triturated with 15 mL of H_2O and the resulting precipitate was filtered and stirred with 0.25% aqueous HCl for 3–4 min at 0 °C. The precipitate was filtered and washed with H_2O until neutral pH. White solid, mp 123–125 °C. (0.268 g, 32%). ^{1}H NMR (300 MHz, DMSO-d_6): 3.4 (s, 3H), 3.81 (s, 3H), 4.56 (s, 1H), 5.31 (s, 1H), 6.31 (d, *J* = 8.2 Hz, 2H), 6.9–7.0 (m, 3H), 7.14–7.21 (m, 3H), 7.84 (d, *J* = 7.3 Hz, 2H). ν_{max}(KBr)/cm^{-1} 3271, 1740, 1718, 1660. MS (EI) *m*/*z*: 353 [M$^+$]. Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.61; H, 5.60; N, 4.31.