PREPARATION OF ENAMINES FROM THE CONDENSATION OF GLYCINE ESTERS WITH NITRO-HETEROCYCLIC ALDEHYDES

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Abstract - In order to prepare the imine derived from condensation of glycine ethyl ester and 5-nitrothiophene-2-carboxaldehyde, another compound was obtained instead. This product was the enamine, ethyl 2-amino-3-(5-nitro-2-thienyl)-2-propenoate, resulting from the condensation between the methylene of the glycine derivative and the heterocyclic carbonyl group. The reactivity of related amines and heterocyclic aldehydes was studied in order to get more insight about the mechanism of enamine formation. It was found that the nitro-heterocyclic group and the easy of enolization of the aminoacidic ester played an important role.

INTRODUCTION

As part of a program directed towards the rational design and synthesis of drugs,[1] we were interested in the preparation of imines of structure **(I)** (Figure **1**). The formation of the C=N linkage from heteroaromatic aldehydes is well documented.[2-4] In addition, the use of glycine as the *N*-containing unit is known.[5-10] Consequently, from a number of general methods of imine synthesis,[11-13] we chose the condensation between heteroaromatic aldehydes with glycine esters to obtain structures of type **(I)**, as shown in Figure **1**. The high yielding preparation of Schiff bases is not always an easy task. In general, the synthesis of aldimines is more difficult than that of ketimines due to the lower stability and acidity of these compounds.[8,14] In our case an additional concern was related to the sensitivity of the starting heterocyclic aldehyde, which made the choice of the reaction conditions a crucial point. A number of conditions have been reported for the condensation of glycine derivatives with carbonyl compounds, namely in CH_2Cl_2 at room temperature using triethylamine and anhydrous magnesium sulfate,[7] in refluxing xylenes using a catalytic amount of boron trifluoride etherate,[8] in methanol at room temperature using triethylamine,[4] and in refluxing pyridine.[5] However, regardless of the reaction conditions used, we found that the main product of the condensation reaction was

enamine **(II)** instead of imine **(I)**, (Figure 1).

In this paper we report on the study performed in order to obtain more information about this product and the process involved in its formation.

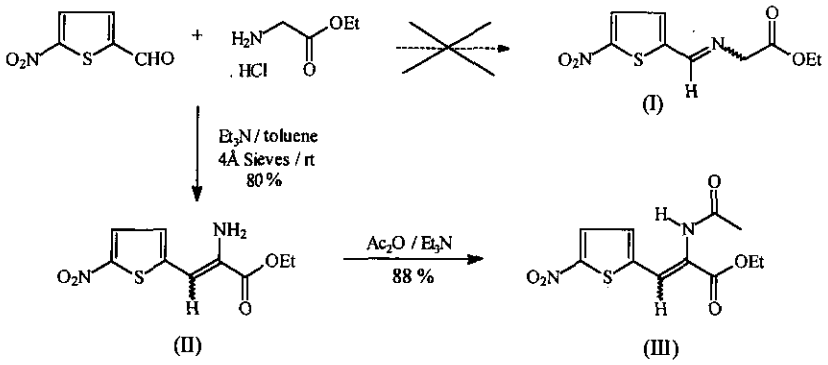
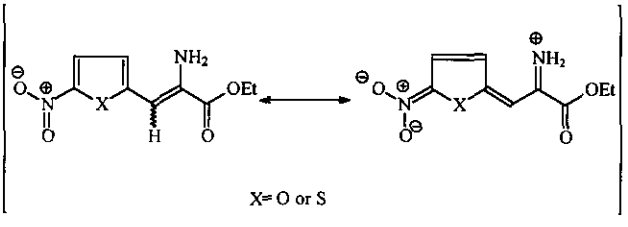


Figure 1

RESULTS AND DISCUSSION

The condensation between 5-nitrothiophene-2-carboxaldehyde and the glycine ester hydrochloride was performed under the conditions previously reported in the literature and cited above,[4,5,7,8] along with some modifications to account for the sensitivity of the starting aldehyde. After extensive experimentation, the best yield was obtained in toluene at room temperature, using triethylamine and 4 Å molecular sieves to trap the water formed during the reaction. Under these experimental conditions, enamine **(II)** was the only product, isolated with a reproducible yield of 80%, being the rest unreacted glycine ester and polymeric materials. The structure of **II** was determined by spectroscopic methods (^{1}H-NMR, ^{13}C-NMR, IR, MS) and elemental microanalysis, as well as by functionalization to its corresponding *N*-acetyl derivative **(III)**, (Figure 1).

In addition, enamine **(II)** showed an intense solvent chromicity effect, characteristic of a cyanine chromophore.[15] In this case the observed color in solution shifts from a deep green in petroleum ether to orange-red in methanol, and the delocalization between electron-donating and electron-accepting groups occurs through a conjugated system of three double bonds:



The unexpected outcome of this condensation prompted us to perform several experiments in order to improve our insight on this reaction (see Figure 2). In this regard, the nature of both the aldehyde and the

amine was changed, trying to identify the factors responsible for this reactivity. In a first step the heterocyclic aldehyde was changed. Using 5-nitro-2-furaldehyde instead of the thiophene ring afforded the same type of enamine **(IV)**, the structure of which was determined by ^{1}H-NMR, IR, and MS spectroscopy. This compound displayed an intense solvent chromicity effect, stronger than that corresponding to **II** (from a blue-green in petroleum ether to deep red in methanol). The condensation between 5-nitro-2-furaldehyde and glycine ester hydrochloride was tried over a wide range of experimental conditions, varying solvents (ranging from toluene to the most polar pyridine), acid or base catalysis and temperature (see **Table 1**). In all cases the isolated yields of enamine **(IV)** were poor. The highest was 50%, corresponding to a 24 h-condensation, run in toluene at room temperature in the presence of triethylamine, and took place before the starting aldehyde was consumed. The enamine seemed to be unstable in the reaction conditions, as seen for a lower yield (10%) obtained at longer reation times (72 h). Under the same conditions, the isolated yields of **IV** were consistently lower than those obtained for enamine **(II)**, thus indicating the enhanced sensitivity of the nitrofuran residue of **IV** to the reaction conditions.

Table 1- Experimental conditions for the condensation between ethyl glycinate hydrochloride and 5-nitro-2-furaldehyde.

Solvent	Catalyst	Conditions	Time (h)	% (IV)[c]
Toluene	*p*-TsOH	reflux[a]	10	17
Toluene	*p*-TsOH	reflux[a]	26	23
Toluene	*p*-TsOH	reflux[a]	48	20
Toluene	Et_3N (1 eq.)	reflux[a]	16.5	15
Toluene	Et_3N (1 eq.)	reflux[a]	24	23
Toluene	Et_3N (1 eq.)	reflux[a]	48	20
Toluene	K_2CO_3 (1%)	reflux[a]	16.5	15
Toluene	K_2CO_3 (1%)	reflux[a]	24	10
Pyridine	------	reflux	17	30
Pyridine	------	reflux	24	8
Toluene	Et_3N (1 eq.)	rt	24	50
Toluene	Et_3N (1 eq.)	rt	72	10[b]
Pyridine	------	rt	72	9[b]
Methylene chloride	Et_3N (1 eq.)	rt	24	6
Methanol	Et_3N (1 eq.)	rt	24	30

a - *Dean-Stark system.* b - *In presence of BHT to inhibit radical polymerization.* c - Corresponds to isolated yields.

Another experiment consisted of the change of the α-amino acid ester residue. To prevent enamine formation the possibility of enolization has to be avoided, and thus the methyl ester of 2-methylalanine, which lacks of enolizable hydrogens, was used. This amino ester gave the corresponding imine **(V)** in good yields and through a much cleaner reaction when submitted to similar conditions (Figure 2).

In other experiment, the amino group was changed from the α- to the β-position, in order to decrease the amino ester nucleophilicity at C-2. Again, in this case the corresponding imine **(VI)** was obtained in good yields (Figure 2).

Finally, the influence of the nitro group in the heterocyclic system was studied, since, to our knowledge there are no reports in the literature dealing with condensations of amines with nitroheterocyclic aldehydes. Accordingly, when thiophene-2-carboxaldehyde was reacted with ethyl glycinate hydrochloride, the imine **(VII)** was obtained as an inseparable 1:1 mixture of E,Z-isomers, as determined by ^{1}H-NMR spectroscopy (Figure 2). This compound was proven to be quite sensitive, and all attempts of purification by column chromatography lead to some decomposition into the starting materials. Recently, imine formation in this type of systems had also been reported by Bonet-Delpon *et al.* when working with a non-nitrated heterocyclic aldehyde (furaldehyde). Under their conditions, however, only one isomer was reported.[4]

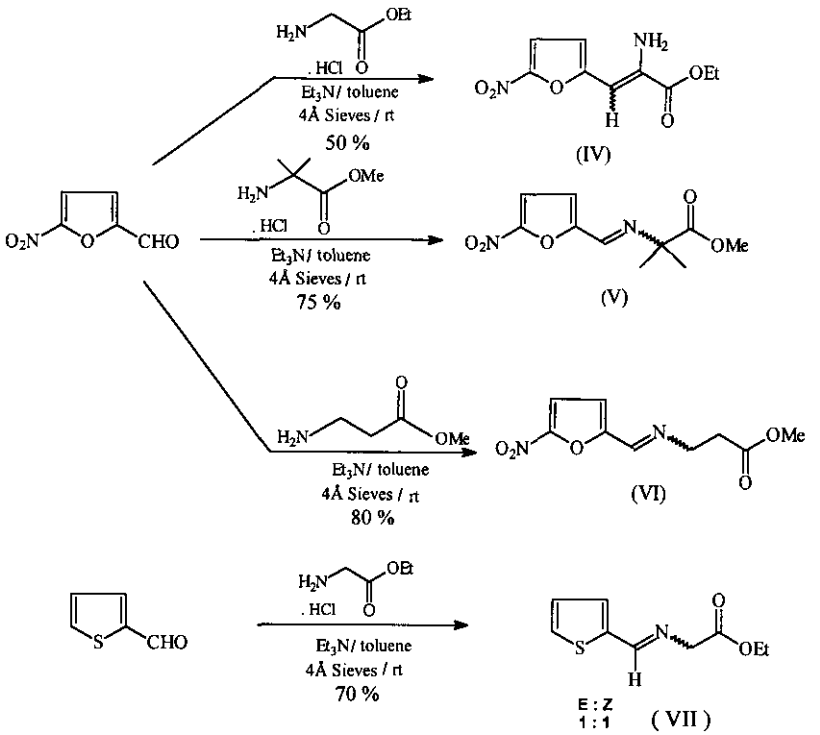


Figure 2

In summary, our results using non-nitrated heterocyclic aldehydes and glycine derivatives follow the expected reaction pattern as reported in the literature.

Conversely, when nitro-heterocyclic aldehydes were used as electrophiles the addition reaction afforded either imines ("normal" mode) or enamines depending on the nature of the amino ester derivative. Imines were formed when enolization was prevented, as for compound **(V)**, or diminished, as for compound **(VI)**. On the other hand, the condensation reaction between glycine esters and nitro-heterocyclic aldehydes gave the corresponding enamines as the sole isolable product, and no imine intermediate was detected. In accordance with these observations the following mechanism is proposed (Figure 3). It is similar to that reported for both the biosynthesis of serine and threonine,[16, 17] and the preparation of serine by condensation of glycinates.[18] The first step is always the expected condensation to give the imine, regardless of the nature

of both amino ester and heterocyclic aldehyde. In the reactions of glycine derivatives with nitro-heterocyclic aldehydes, the newly formed imine is a better nucleophile than the amino ester and attacks to the electrophilic center of either a second molecule of the heteroaromatic aldehyde or the imine itself.[19]

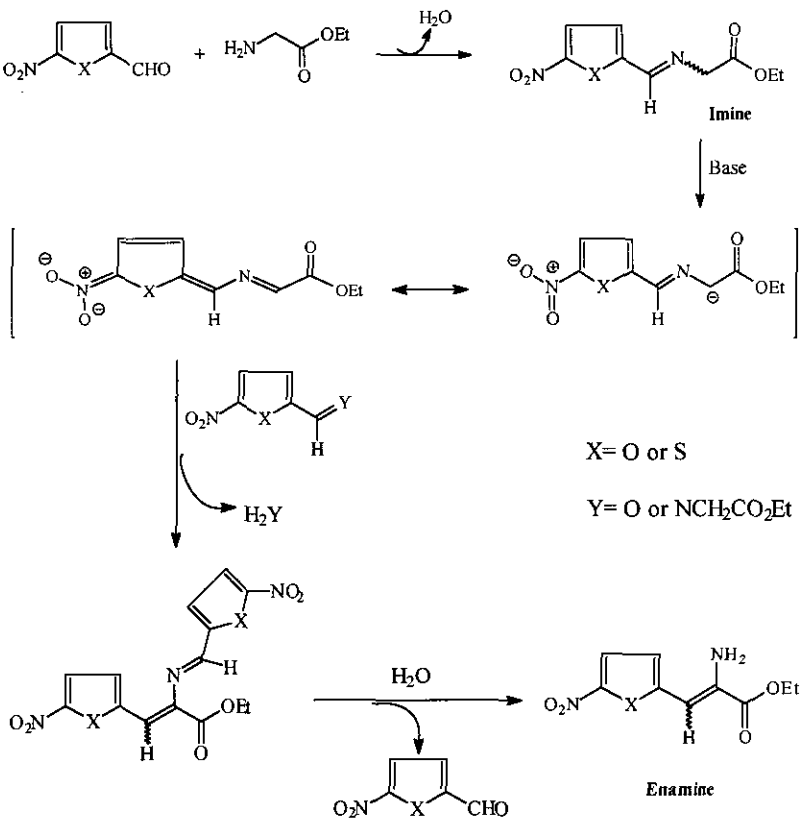


Figure 3

The easy of hydrogen abstraction α to both the *N* atom and the ester group is the reason for the enhanced nucleophilicity. The carbon nitrogen double bond stabilized carbanion resulting from hydrogen abstraction α to the ester is well known and has been used in several alkylation procedures.[20-22] In the reported cases, the formation of the carbanion requires the use of strong bases, such as *t*-BuOK, LDA, or KOH in PTC conditions. In our case, the acidity of this position is increased by the heterocycle containing a suitably positioned nitro group, and thus a weaker base can be used. The lack of any of these activating elements (a nitro group in the heterocyclic ring or an α-ester) renders this position unable to efficiently deprotonate in the presence of triethylamine and act as a nucleophile; as a result, the corresponding imine can be isolated.

We were unable to detect imine as an intermediate of the reaction of glycine derivatives with nitro-heterocyclic aldehydes. This result suggests that deprotonation and further condensation with a second molecule of aldehyde or imine are faster that the formation of the imine itself.

CONCLUSIONS

The reaction of enolizable glycine derivatives with nitro-heterocyclic aldehydes yields the corresponding enamines as the sole isolable products, in either acid or basic conditions. The presence of an electron withdrawing group such as the nitro, capable of further delocalization of the negative charge of an α-enolate, is necessary for the reaction to take place. Conversely, the condensation with non-nitrated heterocyclic aldehydes gives rise to imines, regardless of the nature of the amino ester.

EXPERIMENTAL

5-Nitro-2-furaldehyde, 5-nitrothiophene-2-carboxaldehyde, thiophene-2-carboxaldehyde and glycine ethyl ester hydrochloride are commercially available and were used without further purification. Methylalanine methyl ester hydrochloride and β-alanine methylester hydrochloride were prepared according to literature procedures.[24] All solvents were dried and distilled prior to use.[25] Melting points were determined using a Leitz Microscope Heating Stage Model 350 apparatus and are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorous pentoxide at 3-4 mm Hg, 24 h at rt) and performed on a Fisons EA 1108 CHNS-O analyzer. IR spectra were recorder on a Perkin Elmer 1310 apparatus, using potassium bromide tablets for solid and oil products; the frequencies are expressed in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian XL-100 (at 100 MHz) instrument, Varian Gemini 300 (at 300 MHz and 75 MHz) instrument, with tetramethylsilane as the internal reference and in the indicated solvent; the chemical shifts are reported in ppm. MS were recorded on a Shimadzu GS-MS QP 1100 EX instrument, at 70 eV unless otherwise indicated.

Ethyl 2-amino-3-(5-nitro-2-thienyl)-2-propenoate ***(II)***. To a stirred mixture of 5-nitrothiophene-2-carboxaldehyde (50 mg, 0.32 mmol), triethylamine (0.05 mL, 0.36 mmol), and 4 Å molecular sieves (100 mg) in toluene (2.0 mL), ethyl glycinate hydrochloride (50 mg, 0.36 mmol) was added in three portions. The suspension was stirred 24 h at rt, when the nitro compound was consumed (SiO_2, 20% AcOEt in petroleum ether). The mixture was washed with brine (2x5 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to afford the nitrothiophene derivate as an oily residue, which was purified by chromatography (SiO_2, AcOEt in petroleum ether (0 to 30%)), and recrystallized from chloroform. Green needles. Yield: 62 mg (80%); mp: 86.5-88.5°C. IR: ν_{max} 3330, 1700, 1615, 1510, 1320, 800; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.39 (t, J = 7.2 Hz, 3H), 4.36 (q, J = 7.5 Hz, 2H), 4.79 (br s, 2H), 6.63 (s, 1H), 6.97 (d, J = 4.5 Hz, 1H), 7.90 (d, J = 4.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 Mhz): δ 14.12, 62.46, 100.25, 125.02, 129.51, 134.76, 147.69, 148.74, 164.06; MS: 242 ($M^{+\cdot}$, 100%), 168 ($M^{+\cdot}$-HCO_2Et, 74%). *Anal.* Calcd for $C_9H_{10}N_2O_4S$: C, 44.62; H, 4.16; N, 11.56; S, 13.23. Found: C, 44.45; H, 4.28; N, 11.67; S, 13.37.

Ethyl 2-ethanoylamino-3-(5-nitro-2-thienyl)-2-propenoate (III). A mixture of II (20 mg, 0.08 mmol) and triethylamine (17 μL, 0.12 mmol) in acetic anhydride (1.0 mL) was stirred 3 d at rt, until the enamine was consumed (SiO_2, 20% AcOEt in petroleum ether). Ethyl acetate was added (5 mL) and the mixture was washed with 5% aqueous sodium bicarbonate (3x5 mL), and then brine (2x5 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to afford the nitrothiophene derivative (III) as a solid residue, which was purified by chromatography (SiO_2, AcOEt in petroleum ether (0 to 30%)) and recrystallized from petroleum ether:chloroform. Red-brown needles. Yield: 20 mg (88 %); mp: 216.0-218.0°C. IR: ν_{max} 3448, 1716, 1664, 1506, 1328, 817; ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 1.38 (t, J = 7.0 Hz, 3H), 2.28 (s, 3H), 4.38 (q, J = 7.0 Hz, 2H), 7.10 (br s, 1H), 7.23 (d, J = 4.0 Hz, 1H), 7.70 (s, 1H), 7.90 (d, J = 4.0 Hz, 1H); MS: 284 (M^+, 4%), 242 (M^+- CH_2=C=O, 42%). *Anal.* Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.25; N, 9.85; S, 11.28. Found: C, 46.79; H, 4.04; N, 9.58; S, 11.50.

Ethyl 2-amino-3-(5-nitro-2-furfuryl)-2-propenoate (IV). To a stirred mixture of 5-nitro-2-furaldehyde (280 mg, 2.00 mmol), triethylamine (0.4 mL, 2.00 mmol), and 4 Å molecular sieves (200 mg) in toluene (10.0 mL), ethyl glycinate hydrochloride (280 mg, 2.00 mmol) was added in three portions. The suspension was stirred 24 h at rt, when the nitro compound was consumed (SiO_2, 20% AcOEt in petroleum ether). The mixture was washed with brine (2x10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to afford the nitro derivative as an oily residue, which was purified by chromatography (SiO_2, AcOEt in petroleum ether (0 to 30%)), to give IV. Brown oil. Yield: 226 mg (50%). IR: ν_{max} 3250, 1710, 1620, 1310, 805. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, J = 7.0 Hz, 3H), 4.37 (q, J = 7.0 Hz, 2H), 5.60 (br s, 2H), 6.13 (s, 1H), 6.37 (d, J = 4.0 Hz, 1H), 7.49 (d, J = 4.0 Hz, 1H); MS: 226 (M^+, 70%), 152 (M^+-HCO_2Et, 65%).

Methyl 2-methyl-2-(5-nitro-2-furfurylidenamino)propanoate (V). To a stirred mixture of 5-nitro-2-furaldehyde (200 mg, 1.42 mmol), triethylamine (0.3 mL, 1.50 mmol), and 4 Å molecular sieves (200 mg) in toluene (10.0 mL), 2-methylalanine methyl ester hydrochloride (215 mg, 1.40 mmol) was added in three portions. The suspension was stirred 24 h at rt, when the nitro compound was consumed (SiO_2, 20% AcOEt in petroleum ether). The mixture was washed with brine (2x10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to afford crude nitro derivative as an oily residue, which was purified by chromatography (SiO_2, AcOEt in petroleum ether (0 to 30%)). Brown solid. Yield: 255 mg (75%); mp: 118.0-120.0°C. IR: ν_{max} 17 25, 1685, 1345, 805; ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 1.60 (s, 6H); 3.82 (s, 3H); 7.24 (d, J = 4.0 Hz, 1H); 7.43 (d, J = 4.0 Hz, 1H); 8.25 (s, 1H) ; MS (20 eV): 225 (M^+ - CH_3, 2%), 181 (M^+ - CO_2CH_3, 100%). *Anal.* Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.89; H, 4.88; N, 11.95.

Methyl 3-(5-nitro-2-furfurylidenamino)propanoate (VI). To a stirred mixture of 5-nitro-2-furaldehyde (200 mg, 1.42 mmol), triethylamine (0.2 mL, 1.42 mmol), and 4Å molecular sieves (200 mg) in toluene (5.0 mL),

β-alanine methyl ester hydrochloride (146 mg, 1.42 mmol) was added in three portions. The suspension was stirred 16 h at rt, when the nitro compound was consumed (SiO_2, 20% AcOEt in petroleum ether). The mixture was washed with brine (2x10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to afford the nitro derivative (VI) as an oil, which was purified by chromatography. Yield: 257 mg (80%). IR: ν_{max} 1735, 1680, 1250, 810. ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 2.80 (t, J = 6.0 Hz, 2H), 3.70 (s, 3H), 3.97 (s, J = 6.0 Hz, 2H), 7.03 (d, J = 4.0 Hz, 1H), 7.38 (d, J = 4.0 Hz, 1H), 8.27 (s, 1H); MS: 226 ($M^{+\cdot}$, 6 %).

Ethyl 2-(2-thienylidenamino)ethanoate (VII). To a stirred mixture of thiophene-2-carboxaldheyde (100 mg, 0.89 mmol), triethylamine (0.14 mL, 0.98 mmol), and 4 Å molecular sieves (100 mg) in toluene (2.0 mL), ethyl glycinate hydrochloride (136 mg, 0.98 mmol) was added in three portions. The suspension was stirred at rt until the nitro compound was not present (SiO_2, 20% AcOEt in petroleum ether). The mixture was washed with brine (2x10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to afford the thiophene derivative (VII) as an oil. An analytically pure sample was obtained by column chromatography. Yield: 123 mg (70%). IR: ν_{max} 1725, 1290, 795 cm^{-1}; ^{1}H-NMR (acetone-d_6, 100 MHz): δ 1.22 (t, J = 7.0 Hz, 3H), 4.15 (q, J = 7.0 Hz, 2H), 4.32 (two singlets, corresponding to two stereoisomers, 2H), 7.13 (dd, J = 4.0 and 4.5 Hz, 1H), 7.47 (dd, J = 1.0 and 4.0 Hz, 1H), 7.60 (dt, J = 1.0 and 4.5 Hz, 1H), 8.48 (two singlets, corresponding to two stereoisomers, 1H); MS: 197 ($M^{+\cdot}$, 15%).

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