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Tetrahedron
Tetrahedron 62 (2006) 1345–1350

Synthesis of stable azomethine ylides by the rearrangement of 1,3-dipolar cycloadducts of 3,4-dihydroisoquinoline-2-oxides with DMAD

Necdet Coşkun* and Selen Tunçman

Department of Chemistry, Uludağ University, 16059 Bursa, Turkey

Received 7 August 2005; revised 31 October 2005; accepted 17 November 2005

Available online 9 December 2005

Abstract—1-Aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines were prepared according to a one-pot procedure involving the reaction of 2-(3,4-dimethoxyphenyl)-ethylamine with aromatic aldehydes in TFA at reflux. The tetrahydroisoquinolines were treated with H_2O_2–WO_4^{2-} in methanol at room temperature to give the corresponding 3,4-dihydroisoquinoline-2-oxides. Treatment of these cyclic nitrones with DMAD in toluene at room temperature gave the corresponding isoxazolo[3,2-*a*]isoquinolines. These compounds were heated in toluene at reflux to give the corresponding ylides in high yields (Method A). The effect of the substituents on the rate of the rearrangement of such compounds prompted us to discuss a new mechanism involving consecutive C–C bond heterolysis and 1,3-sigmatropic shift. A one-pot reaction involving the treatment of the nitrones with equimolar amounts of DMAD in refluxing toluene also gave the ylides (Method B). The structures of the prepared compounds were elucidated by spectral means and elemental analyses.

1. Introduction

The synthetic utility of the 1,3-dipolar cycloaddition reaction is evident from the number and the scope of targets that can be prepared by this chemistry. Nitrones are the most useful through their ability to generate nitrogen- and oxygen based functionality from the cycloadducts.[1] The cycloadducts of di- and triarylimidazoline 3-oxides[2] with a variety of dipolarophiles[3] give bicyclic compounds with potentially interesting biological activity.[4] On the other hand, they are a source of new heterocyclic compounds via interesting ring-opening reactions.[5]

Previously, we reported the synthesis of stable adducts of Δ^3-imidazoline 3-oxides with DMAD[3d,e] and 3-phenylpropanoic acid alkyl esters.[3f] Thermally and base-induced ring-opening reactions of these adducts were demonstrated. As a continuation of our interest in the ring-opening reactions of 4-isoxazolines,[3d,e] we prepared 1-aryl-3,4-dihydroisoquinoline-2-oxides from the oxidation of 1-aryl-1,2,3,4-tetrahydroisoquinolines under the conditions recently reported[6] and their adducts with DMAD. It is known that nitrones react with alkynes to give generally unstable adducts or those, which are stable can be subjected to rearrangements under thermal conditions. Rearrangements of DMAD adducts of some heterocyclic *N*-oxides has been reviewed.[1a] 4,5-Dihydroimidazole *N*-oxides undergo 1,3-dipolar cycloaddition with alkyne dipolarophiles and the cycloadducts were shown to convert to the corresponding ene-1,1-diamines.[7] The thermal reaction of some 4-isoxazoline derivatives leading to isoquinoline-fused pyrroles has been investigated and it was found that the pathway of the rearrangement to pyrroles is consistent with a route involving an acylaziridine.[8]

2. Results and discussion

We report herein the synthesis of 1-aryltetrahydroisoquinolines **2a–e** and their oxidation with H_2O_2–WO_4^{2-} in methanol at room temperature to give cyclic nitrones **3a–e**. Isolated or in situ formed 8,9-dimethoxy-10b-aryl-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl esters **4a–e** were shown to undergo substituent–dependent rearrangement to novel stable 3,4-dihydroisoquinolinium *N*-ylides **5a–e** (Scheme 1). The results are presented in Table 1. A new mechanism involving consecutive C–C bond heterolysis and 1,3-sigmatropic shift is discussed.

Keywords: Isoquinoline; 1-Aryl-1,2,3,4-tetrahydroisoquinoline; THI; Pictet–Spengler; Oxidation with H_2O_2–tungstate; 3,4-Dihydroisoquinoline-2-oxide; Rearrangement; Isoxazoloisoquinoline; Stable azomethine ylide; 4-Isoxazoline rearrangement mechanism; Alkyne; DMAD; Dipolar cycloaddition; Synthesis; Heterocycles.
* Corresponding author. Tel.: +90 44292561308; fax: +90 4428022; e-mail: coskun@uludag.edu.tr

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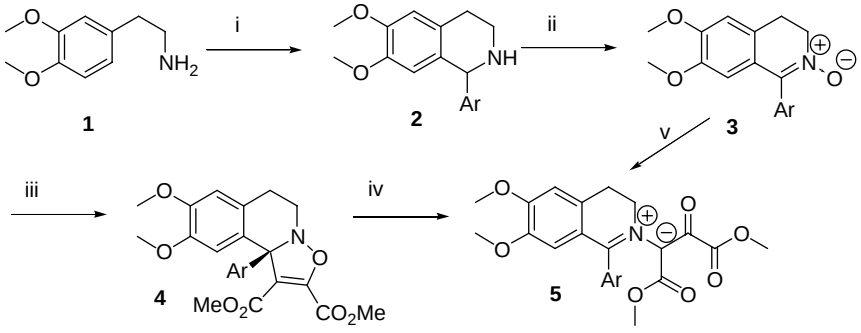
doi:10.1016/j.tet.2005.11.040

Table 1. Synthesis of compounds **2a–e**, **3a–e** and **4a–e**

1–5	Ar	Yield (%)		
		2	**3**	**4**
a	Ph	70[a]	43[b]	95[c]
b	3,4 $(MeO)_2C_6H_3$	85	50	97
c	3-$NO_2C_6H_4$	80	40	96
d	4-ClC_6H_4	70	69	98
e	3,4 $(OCH_2O)C_6H_3$	60	45	97

[a] The reaction times were 3, 5.5, 2.5, 5, 5.5 h for **2a**,**b**,**c**,**d**,**e**, respectively.
[b] The reaction times were 5.5, 17.5, 23, 21, 19 for **3a**,**b**,**c**,**d**,**e**, respectively.
[c] The reaction times were 18, 5.5, 24, 18, 15 for **4a**,**b**,**c**,**d**,**e**, respectively.

corresponding nitrones **3a–e** in toluene in the presence of DMAD (see Table 2, Method B). It was shown that isoxazolo[3,2-*a*]isoquinolines convert at different rates to the corresponding ylides **5a–e**. The structure of stable 3,4-dihydroisoquinolinium *N*-ylides **5a–e** was deduced from their elemental analyses and spectral data. The compounds are highly coloured and soluble in diluted acids with loss of their colours. The extraction of the acidic water solutions of ylides **5** with $CHCl_3$ again affords the free ylides **5**. Our preliminary experiments show that they react, as expected, with dipolarophiles such as phenyl isocyanate.



Scheme 1. Reagents and conditions: (i) ArCHO; TFA; reflux; (ii) H_2O_2–Na_2WO_4; MeOH; rt; (iii) DMAD; toluene; rt; (iv) toluene; reflux; (v) DMAD; toluene; reflux.

2-(3,4-Dimethoxyphenyl)-ethylamine **1** was reacted with an equimolar amount of the corresponding aromatic aldehyde in refluxing TFA to give in good yields the corresponding 1-aryl-1,2,3,4-tetrahydroisoquinolines **2a–e**.

Compounds **2** were treated with H_2O_2–WO_4^{2-} in methanol according to a method we have recently reported[6] to give 3,4-dihydroisoquinoline-2-oxides **3a–e**. The products were purified by chromatographic methods and were recrystallized from ethanol–ether (1/3).

Nitrones **3a–e** were reacted with DMAD in toluene at room temperature to give quantitatively the corresponding isoxazolo[3,2-*a*]isoquinolines **4a–e**. The products were purified by recrystallization from ethanol in the cases of **4a**,**c**,**e** and preparative TLC in the cases of **4b**,**d**. The NMR as well as the infra red spectral data for compounds **4a–e** are in good agreement with those we have previously reported for similar adducts.[3d–f] Isolated **4a–e** were refluxed in toluene for the times specified in Table 2 (Method A) to give heretofore unreported exclusively stable azomethine ylides **5a–e**. The methods available for generating azomethine ylides, were discussed in a resent review.[9] The same products resulted from the direct heating of the

Table 2. Synthesis of *N*-ylides **5a–e**

	Yield		Reaction time (h)	
	Method A[a]	Method B[b]	A	B
5a	93	75	11	12
5b	100	74	1.5	1.5
5c	82	95	7	8
5d	91	71	13	14
5e	87	96	4	4.2

[a] Yields are based on the starting **4**.
[b] Yields based on the starting **3**.

On the other hand their reactions with amines as diethylamine lead to the formation of corresponding 3,4-dihydroisoquinoline. The ^{13}C NMR spectroscopic assignments specifically for **5e** are shown in Figure 1.

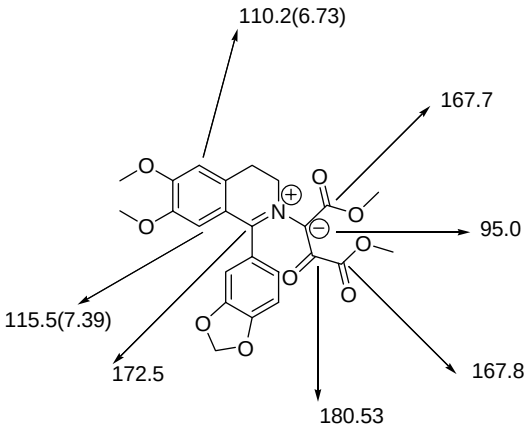
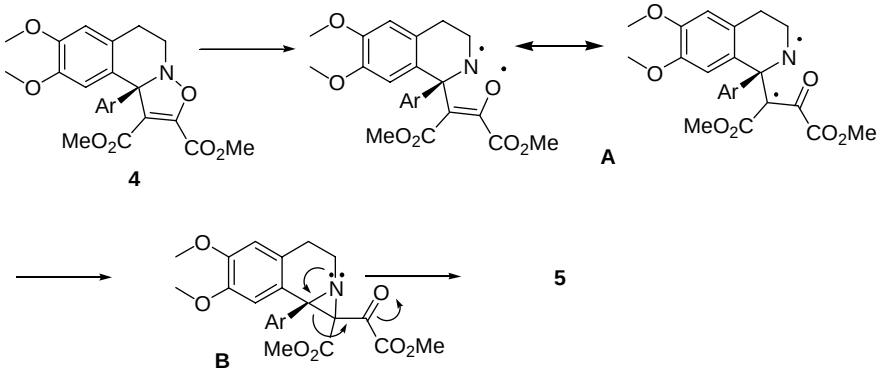


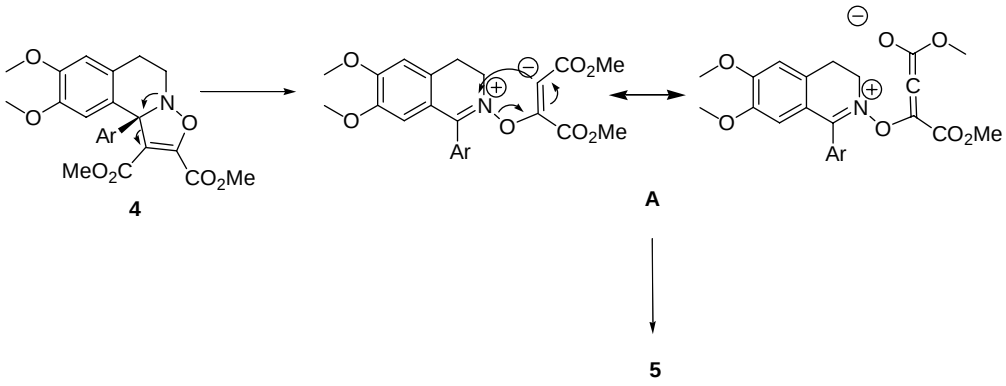
Figure 1. Some ^1H and ^{13}C NMR assignments for compound **5e**.[10]

Electron donating groups on the aromatic ring at C-10b of compounds **4** increase the rate of rearrangement to ylides **5** while electron-withdrawing groups (see Table 2 for the reaction times) decrease it.

Aziridines are generally assumed to be involved in the rearrangements of 4-isoxazolines.[9] A similar approach could be assumed for the conversion of compounds **4** to **5** as depicted in Scheme 2. The homolysis of N–O bond in compounds **4** could give diradicals **A**, which could cyclize to the corresponding aziridines **B**. Thermal ring-opening of aziridine part of **B** could give ylides **5** (see Scheme 2).



Scheme 2. Probable aziridine involving mechanism for the rearrangement of isoxazoloisoquinolines **4**.



Scheme 3. Probable C–C bond heterolysis involving mechanism for the rearrangement of isoxazoloisoquinolines **4**.

However, the pronounced substituent effects discussed above do not support the acylaziridine intermediate in the rearrangement of 4-isoxazolines. It is expected that the substituents on the 10b-phenyl will affect neither homolysis nor heterolysis of the N–O bond in the isoxazoline part of compounds **4**. This prompted us to consider an alternative mechanism outlined in Scheme 3. Electron donating groups on the aromatic ring of **4** probably favour the C-3, C-4 bond heterolysis to give zwitter ions **A** stabilised by resonance, which in turn undergo 1,3-sigmatropic rearrangement to give ylides **5a–e**. The electron donating groups on the aromatic ring at C-10b could stabilise the forming azomethine ylides by their +R effects.

Thus, 1-aryltetrahydroisoquinolines prepared according to Pictet–Spengler procedure from 2-(3,4-dimethoxyphenyl)-ethylamine and the corresponding aromatic aldehydes were oxidized to nitrones **3** the 1,3-dipolar cycloaddition products of which with DMAD were shown to afford previously unknown and stable 3,4-dihydroisoquinolinium *N*-ylides when heated in toluene. A plausible mechanism involving consecutive C–C bond heterolysis and 1,3-sigmatropic shift was discussed.

3. Experimental

Melting points were recorded on an Electrothermal Digital melting point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. NMR spectra were recorded on a Mercury Plus 400 MHz spectrometer. UV/vis spectra of compounds **5a–e** were recorded on a Shimadzu UV-2100 spectrophotometer. TLC controls were performed using silica gel coated aluminium sheets. Chloroform, petroleum ether, methanol and acetone (45:40:10:5) solvent mixture was used as an eluent system. Visualisation was effected with UV light. The elemental analyses were performed on a EuroEA 3000 CHNS analyser.

3.1. Synthesis of 1-aryl-1,2,3,4-tetrahydroisoquinolines 2. General procedure

To a solution of 2-(3,4-dimethoxyphenyl)-ethylamine (5 mmol, 0.9062 g) in TFA (3 mL) the corresponding aldehyde (5 mmol) was added and the solution was refluxed for the time specified in Table 1. The reaction mixture was poured onto ice and basified with sodium hydroxide. The mixture was extracted with chloroform (3×10 mL) and the combined extracts were dried over anhydrous Na_2SO_4. The organic solvent was evaporated under vacuum and the residue was crystallized from ethanol.

3.1.1. 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline 2a. R_f=0.31; yield 0.943 g, 70%; mp 110–111 °C; IR (KBr) ν_{NH} 3328 cm^{-1}. (400 MHz, $CDCl_3$): δ 1.87 (1H, s), 2.64–2.71 (1H, m), 2.82–2.90 (1H, m), 2.94–2.99 (1H, m), 3.11–3.17 (1H, m), 3.55 (3H, s), 3.79 (3H, s), 4.97 (1H, s), 6.17 (1H, s), 6.56 (1H, s), 7.17–7.26 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7; 42.3; 56.3; 56.4; 61.9; 111.4; 111.9; 127.8; 128.1; 128.8;

129.3; 130.3; 145.3; 147.5; 148.1. Anal. Calcd for $C_{17}H_{19}NO_2$ (269.34) C, 75.81; H, 7.11; N, 5.20; Found C, 75.75; H, 7.20; N, 5.30.

3.1.2. 1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 2b. $R_f=0.23$; yield 85%; mp 88–89 °C; IR (KBr) ν_{NH} 3567 cm^{-1}. (400 MHz, $CDCl_3$): δ 1.83 (1H, s), 2.71–2.77 (1H, m), 2.92–2.99 (1H, m), 3.03–3.1 (1H, m), 3.22–3.28 (1H, m), 3.66 (3H, s), 3.84 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 4.99 (1H, s), 6.28 (1H, s), 6.63 (1H, s), 6.78–6.83 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3; 42.2; 55.8; 55.8; 55.9; 56.0; 61.5; 110.7; 110.9; 111.4; 111.8; 121.3; 127.6; 130.1; 137.3; 147.0; 147.6; 148.3; 149.0. Anal. Calcd for $C_{19}H_{23}NO_4$ (329.39) C, 69.28; H, 7.04; N, 4.25; Found C, 69.35; H, 6.88; N, 4.23.

3.1.3. 6,7-Dimethoxy-1-(3-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline 2c. $R_f=0.15$; yield 1.257 g, 80%; mp 109–111 °C; IR (KBr) ν_{NH} 3312 and 3256 cm^{-1}. (400 MHz, $CDCl_3$): δ 1.77 (1H, s), 2.73–2.79 (1H, m), 2.91–2.98 (1H, m), 3.04–3.10 (1H, m), 3.14–3.20 (1H, m), 3.64 (3H, s), 3.89 (3H, s), 5.16 (1H, s), 6.17 (1H, s), 6.66 (1H, s), 7.49 (1H, t, $J=7.6$ Hz), 7.61 (1H, d, $J=7.6$ Hz), 8.12–8.17 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.1; 41.6; 55.8; 55.9; 60.7; 110.7; 111.8; 122.5; 123.8; 127.9; 128.2; 129.3; 135.2; 147.2; 147.3; 148.1; 148.4. Anal. Calcd for $C_{17}H_{18}N_2O_4$ (314.34) C, 64.96; H, 5.77; N, 8.91; Found C, 64.94; H, 5.75; N, 9.02.

3.1.4. 1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 2d. $R_f=0.54$; yield 1.063 g, 70%; mp 103–105 °C; IR (KBr) ν_{NH} 3242 cm^{-1}. (400 MHz, $CDCl_3$): δ 1.81 (1H, s), 2.71–2.77 (1H, m), 2.88–2.96 (1H, m), 3.01–3.07 (1H, m), 3.16–3.22 (1H, m), 3.64 (3H, s), 3.87 (3H, s), 5.02 (1H, s), 6.20 (1H, s), 6.63 (1H, s), 7.20 (2H, d, $J=8.0$ Hz), 7.29 (2H, d, $J=8.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.2; 41.8; 55.8; 55.9; 60.8; 110.8; 111.5; 127.7; 128.5; 129.3; 130.3; 133.1; 143.4; 147.1; 147.8. Anal. Calcd for $C_{17}H_{18}ClNO_2$ (303.78) C, 67.21; H, 5.97; N, 4.61; Found C, 67.10; H, 5.97; N, 4.75.

3.1.5. 1-Benzo[1,3]dioxol-5-yl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 2e. $R_f=0.37$; yield 0.940 g, 60%; mp 133–134 °C; IR (KBr) ν_{NH} 3252 cm^{-1}. (400 MHz, $CDCl_3$): δ 1.76 (1H, s), 2.70–2.75 (1H, m), 2.88–2.95 (1H, m), 3.0–3.06 (1H, m), 3.19–3.24 (1H, m), 3.67 (3H, s), 3.87 (3H, s), 4.97 (1H, s), 5.94 (2H, s), 6.28 (1H, s), 6.62 (1H, s), 6.71–6.77 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3; 41.9; 55.8; 55.9; 61.2; 101.0; 107.9; 109.2; 110.9; 111.42; 122.2; 127.7; 129.9; 139.1; 146.8; 147.1; 147.7; 147.7. Anal. Calcd for $C_{18}H_{19}NO_4$ (313.35) C, 68.99; H, 6.11; N, 4.47; Found C, 68.90; H, 5.99; N, 4.55.

3.2. Synthesis of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-oxides 3a–e. General procedure

To a solution of tetrahydroisoquinoline **2** (0.5 mmol) in methanol (10 mL) H_2O_2 (35%, 2 mmol) was added in the presence of $Na_2WO_4\cdot H_2O$ (0.025 mmol, 8.3 mg). The reaction mixture was stirred at room temperature for the specified time. The solvent was evaporated and water (15 mL) was added to the residue and extracted with chloroform (3×10 mL). The combined extracts were dried and the solvent evaporated. The purification was performed by preparative TLC using silica gel as adsorbent and chloroform, petroleum ether, methanol and acetone (45:40:10:5) solvent mixture as an eluent.

3.2.1. 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-oxide 3a. $R_f=0.51$; yield 0.061 g, 43%; mp 156–157 °C; IR (KBr) $\nu_{C=N}$ 1590 cm^{-1}; ν_{N-O} 1286 cm^{-1}. (400 MHz, $CDCl_3$): δ 3.15 (2H, t, $J=7.6$ Hz), 3.62 (3H, s), 3.91 (3H, s), 4.26 (2H, t, $J=7.6$ Hz), 6.36 (1H, s), 6.76 (1H, s), 7.43–7.49 (3H, m), 7.56 (2H, d, $J=7.02$ Hz). (100 MHz, $CDCl_3$): δ 27.9; 56.3; 56.4; 59.8; 110.5; 110.6; 123.6; 125.7; 128.5; 129.6; 130.4; 131.4; 142.3; 147.9; 149.6. Anal. Calcd for $C_{17}H_{17}NO_3$ (283.32) C, 72.07; H, 6.05; N, 4.94; Found C, 72.05; H, 5.99; N, 4.97.

3.2.2. 1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline *N*-oxide 3b. $R_f=0.28$; yield 0.086 g, 50%; mp 165–166 °C; IR (KBr) $\nu_{C=N}$ 1590 cm^{-1}; ν_{N-O} 1283 cm^{-1}. (400 MHz, $CDCl_3$): δ 3.14 (2H, t, $J=7.2$ Hz), 3.65 (3H, s), 3.87 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 4.24 (2H, t, $J=7.2$ Hz), 6.45 (1H, s), 6.75 (1H, s), 6.95 (1H, d, $J=8.4$ Hz), 7.13 (1H, d, $J=8.4$ Hz) 7.20 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9; 56.1; 56.2; 56.3; 56.4; 59.8; 110.6; 110.8; 111.8; 113.5; 123.5; 123.6; 123.7; 125.9; 142.3; 147.9; 148.7; 149.6; 149.9. Anal. Calcd for $C_{19}H_{21}NO_5$ (343.37) C, 66.46; H, 6.16; N, 4.08; Found C, 66.40; H, 6.34; N, 4.06.

3.2.3. 6,7-Dimethoxy-1-(3-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline *N*-oxide 3c. $R_f=0.54$; yield 0.066 g, 40%; mp 172–173 °C; IR (KBr) $\nu_{C=N}$ 1584 cm^{-1}; ν_{N-O} 1284 cm^{-1}. (400 MHz, $CDCl_3$): δ 3.20 (2H, t, $J=7.6$ Hz), 3.65 (3H, s), 3.95 (3H, s), 4.29 (2H, t, $J=7.6$ Hz), 6.31 (1H, s), 6.81 (1H, s), 7.69 (1H, t, $J=8.0$ Hz), 8.01 (1H, d, $J=8.0$ Hz), 8.30 (1H, d, $J=8.0$ Hz), 8.51 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6; 56.2; 56.3; 59.9; 109.8; 110.8; 122.2; 124.2; 125.6; 125.7; 129.3; 132.8; 136.6; 139.7; 148.0; 148.1; 149.9. Anal. Calcd for $C_{17}H_{16}N_2O_5$ (328.32) C, 62.19; H, 4.91; N, 8.53; Found C, 62.10; H, 4.95; N, 8.66.

3.2.4. 1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline *N*-oxide 3d. $R_f=0.56$; yield 0.110 g, 69%; mp 216–217 °C; IR (KBr) $\nu_{C=N}$ 1595 cm^{-1}; ν_{N-O} 1284 cm^{-1}. (400 MHz, $CDCl_3$): δ 3.15 (2H, t, $J=7.6$ Hz), 3.65 (3H, s), 3.92 (3H, s), 4.25 (2H, t, $J=7.6$ Hz), 6.35 (1H, s), 6.76 (1H, s), 7.45 (2H, d, $J=8.4$ Hz), 7.57 (2H, d, $J=8.4$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9; 56.3; 56.4; 59.9; 110.3; 110.7; 123.1; 125.8; 128.8; 129.7; 132.0; 135.5; 141.3; 148.1; 149.7. Anal. Calcd for $C_{17}H_{16}ClNO_3$ (317.77) C, 64.26; H, 5.08; N, 4.41; Found C, 64.40; H, 5.03; N, 4.42.

3.2.5. 1-Benzo[1,3]dioxol-5-yl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline *N*-oxide 3e. $R_f=0.56$; yield 0.074 g, 45%; mp 169–170 °C; IR (KBr) $\nu_{C=N}$ 1590 cm^{-1}; ν_{N-O} 1288 cm^{-1}. (400 MHz, $CDCl_3$): δ 3.13 (2H, t, $J=8.0$ Hz), 3.68 (3H, s), 3.91 (3H, s), 4.23 (2H, t, $J=8$ Hz), 6.02 (2H, s), 6.44 (1H, s), 6.74 (1H, s), 6.89 (1H, d, $J=8.0$ Hz), 6.98 (1H, d, $J=8.0$ Hz), 7.16 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9; 56.3; 56.4; 59.8; 101.6; 108.4; 110.5; 110.7; 111.0; 123.6; 123.7; 124.7; 125.8; 141.9; 147.7; 147.9; 148.6; 149.6. Anal. Calcd for $C_{18}H_{17}NO_5$ (327.33) C, 66.05; H, 5.23; N, 4.28; Found C, 66.00; H, 5.20; N, 4.08.

3.3. Synthesis of isoxazolo[3,2-*a*]isoquinolines 4a–e. General procedure

To a solution of nitrone **3** (0.15 mmol) in toluene (10 mL) DMAD (0.225 mmol, 0.032 g) was added and the reaction mixture stirred for the specified time. The solvent was evaporated under vacuum and the residue crystallized from ethanol in the cases of **4a**,**c**,**e**. Compounds **4b**,**d** were purified by preparative TLC.

3.3.1. 8,9-Dimethoxy-10b-phenyl-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl ester 4a. R_f=0.22; yield 0.061 g, 95%; mp 124–125 °C; IR (KBr) $\nu_{C=O}$ 1758; 1712 cm^{-1}; $\nu_{C=C}$ 1626 cm^{-1}. (400 MHz, $CDCl_3$): δ 2.64–2.70 (1H, m), 3.14–3.22 (1H, m), 3.26–3.33 (1H, m), 3.64–3.72 (1H, m), 3.66 (3H, s), 3.68 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 6.63 (1H, s), 6.99 (1H, s), 7.27–7.37 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8; 47.1; 52.2; 53.4: 56.0; 56.1; 77.3; 110.8; 112.3; 114.9; 126.6; 126.8; 128.2; 128.3; 129.1; 142.8; 147.7; 148.5; 153.5; 159.8; 163.6. Anal. Calcd for $C_{23}H_{23}NO_7$ (425.43) C, 64.93; H, 5.45; N, 3.29; Found C, 65.10; H, 5.55; N, 3.40.

3.3.2. 10b-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl ester 4b. R_f=0.89; yield 0.071 g, 97%; oil; IR (KBr) $\nu_{C=O}$ 1758; 1712 cm^{-1}; $\nu_{C=C}$ 1626 cm^{-1}. (400 MHz, $CDCl_3$): δ 2.60–2.70 (1H, m), 3.15–3.22 (1H, m), 3.24–3.32 (1H, m), 3.64–3.72 (1H, m), 3.67 (3H, s), 3.71 (3H, s), 3.79 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 6.62 (1H, s), 6.76 (1H, d, J=8.4 Hz), 6.82 (1H, dd, J=8.4, 2.0 Hz), 6.96 (1H, d, J=2.0 Hz), 7.04 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7; 46.9; 52.3; 53.3: 56.0; 56.1; 77.0; 110.4; 110.8; 112.3; 112.4; 115.7; 121.9; 126.6; 126.7; 135.0; 147.6; 148.4; 148.7; 149.0; 152.9; 159.7; 163.8. Anal. Calcd for $C_{25}H_{27}NO_9$ (485.48) C, 61.85; H, 5.61; N, 2.89; Found C, 61.80; H, 5.63; N, 2.89.

3.3.3. 8,9-Dimethoxy-10b-(3-nitrophenyl)-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl ester 4c. R_f=0.79; yield 0.068 g, 96%; mp 123–124 °C; IR (KBr) $\nu_{C=O}$ 1758; 1719 cm^{-1}; $\nu_{C=C}$ 1644 cm^{-1}. (400 MHz, $CDCl_3$): δ 2.72–2.77 (1H, m), 3.15–3.24 (1H, m), 3.25–3.31 (1H, m), 3.64–3.72 (1H, m), 3.67 (3H, s), 3.70 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 6.65 (1H, s), 6.89 (1H, s) 7.50 (1H, t, J=8.2 Hz), 7.8 (1H, d, J=8.2 Hz), 8.16 (1H, d, J=8.2 Hz), 8.25 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9; 47.3; 52.5; 53.5: 56.1; 77.2; 111.2; 111.6; 114.1; 123.3; 124.1; 125.2; 126.8; 129.3; 135.2; 145.5; 148.1; 148.3; 148.9; 153.9; 159.5; 163.4. Anal. Calcd for $C_{23}H_{22}N_2O_9$ (470.43) C, 58.72; H, 4.71; N, 5.95; Found C, 58.80; H, 4.90; N, 6.10.

3.3.4. 10b-(4-Chlorophenyl)-8,9-dimethoxy-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl ester 4d. R_f=0.74; yield 0.068 g, 98%; oil; IR (KBr) $\nu_{C=O}$ 1755; 1709 cm^{-1}; $\nu_{C=C}$ 1638 cm^{-1}. (400 MHz, $CDCl_3$): δ 2.63–2.0 (1H, m), 3.12–3.20 (1H, m), 3.23–3.30 (1H, m), 3.64–3.72 (1H, m), 3.67 (3H, s), 3.69 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 6.62 (1H, s), 6.95 (1H, s), 7.28–7.32 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8; 47.2; 52.3; 53.4; 56.0; 56.1; 76.8; 110.9; 112.1; 114.6; 126.2; 126.8; 128.5; 130.5; 134.2; 141.5; 147.9; 148.7; 153.6; 159.7; 163.5. Anal. Calcd for $C_{23}H_{22}ClNO_7$ (459.88) C, 60.07; H, 4.82; N, 3.05; Found C, 60.10; H, 4.83; N, 3.10.

3.3.5. 10b-Benzo[1,3]dioxol-5-yl-8,9-dimethoxy-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylic acid dimethyl ester 4e. R_f=0.86; yield 0.068 g, 97%; mp 122–123 °C; IR (KBr) $\nu_{C=O}$ 1749; 1716 cm^{-1}; $\nu_{C=C}$ 1637 cm^{-1}. (400 MHz, $CDCl_3$): δ 2.61–2.67 (1H, m), 3.12–3.18 (1H, m), 3.25–3.32 (1H, m), 3.66–3.77 (1H, m), 3.67 (3H, s), 3.71 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 5.93 (2H, s), 6.60 (1H, s), 6.75 (1H, d, J=8.4 Hz), 6.78 (1H, d, J=8.4 Hz), 6.88 (1H, s) 7.02 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7; 46.9; 52.2; 53.3: 56.0; 56.1; 77.1; 101.5; 107.8; 109.7; 110.8; 112.2; 114.9; 122.9; 126.6; 126.7; 136.8; 147.5; 147.7; 147.8; 148.5; 153.4; 159.8; 163.6. Anal. Calcd for $C_{24}H_{23}NO_9$ (469.44) C, 61.40; H, 4.94; N, 2.98; Found C, 61.50; H, 5.10; N, 3.10.

3.4. Synthesis of azomethine ylides 5a–e. Method A; General procedure

A solution of compound **4** (0.1 mmol) in toluene (5 mL) was refluxed for the specified time (see Table 2). The solvent was evaporated under vacuum and the residue subjected to a silica gel coated TLC plate and eluted with chloroform, petroleum ether, methanol and acetone (45:40:10:5) solvent mixture. The isolated product was crystallized from ethanol ether mixture (1:5).

3.5. Synthesis of azomethine ylides 5a–e. Method B; General procedure

To a solution of nitrone **3** (0.2 mmol) dissolved in toluene (10 mL) DMAD was added and the mixture refluxed for the specified time. The solvent was evaporated and the mixture was subjected on a preparative TLC plate coated with silica gel. The isolated coloured compounds were crystallized from ethanol ether mixture (1:5).

3.5.1. Azomethine ylide 5a. R_f=0.5; yield; Method A, 0.040 g, 93%; Method B, 0.064 g, 75%; light red coloured crystals; mp 228–229 °C; IR (KBr) $\nu_{C=O}$ 1726; 1664 cm^{-1}. UV/vis λ_{max} $CHCl_3$ nm: 256.5, 313.5, 361.5, 455.1; (400 MHz, $CDCl_3$): δ 3.25 (2H, t, J=7.4 Hz), 3.52 (3H, s), 3.63 (3H, s), 3.69 (3H, s), 4.16 (3H, s), 4.01–4.21 (1H, m), 4.25–4.30 (1H, m), 6.57 (1H, s), 6.86 (1H, s), 7.44–7.53 (5H, m). (100 MHz, $CDCl_3$): δ 26.9; 50.8; 52.0; 54.3; 56.3; 56.8; 95.5; 110.5; 115.5; 121.0; 128.2; 128.5; 131.8; 131.9; 134.7; 148.3; 156.1; 164.3; 168.6; 171.1; 174.9. Anal. Calcd for $C_{23}H_{23}NO_7$ (425.43) C, 64.93; H, 5.45; N, 3.29; Found C, 64.98; H, 5.60; N, 3.40.

3.5.2. Azomethine ylide 5b. R_f=0.47; yield; Method A, 0.049 g, 100%; Method B, 0.072 g, 74%; dark orange crystals; mp 128–129 °C; IR (KBr) $\nu_{C=O}$ 1725; 1665 cm^{-1}. UV/vis λ_{max} $CHCl_3$ nm: 255.5, 391.5; (400 MHz, $CDCl_3$): δ 3.13 (2H, t, J=6.4 Hz), 3.37 (3H, s), 3.71 (3H, s), 3.87 (6H, s), 3.88 (3H, s), 3.98 (3H, s), 4.16 (2H, t, J=6.4 Hz), 6.76 (1H, s), 6.86 (1H, d, J=9.2 Hz), 6.91 (1H, d, J=9.2 Hz), 6.98 (1H, s), 7.45 (1H, s). (100 MHz, $CDCl_3$): δ 26.6; 50.5; 51.8; 53.1; 56.0; 56.1; 56.2; 56.4; 96.1; 107.5; 109.9; 110.8; 115.3; 115.6; 121.9; 132.2; 139.1; 148.1; 148.6; 148.9; 154.8; 167.2; 167.6; 172.1; 180.3. Anal. Calcd for

$C_{25}H_{27}NO_9$ (485.48) C, 61.85; H, 5.61; N, 2.89; Found C, 61.90; H, 5.75; N, 3.00.

3.5.3. Azomethine ylide 5c. R_f=0.59; yield; Method A, 0.039 g, 82%; Method B, 0.090 g, 95%; dark red crystals; mp 213–214 °C; IR (KBr) $\nu_{C=O}$ 1735; 1688 cm^{-1}. UV/vis λ_{max} $CHCl_3$ nm: 228.0, 233.0, 259.0, 315.5, 372.0, 469.0; (400 MHz, $CDCl_3$): δ 3.16–3.24 (1H, m), 3.31–3.40 (1H, m), 3.59 (3H, s), 3.63 (3H, s), 3.65 (3H, s), 4.03 (3H, s), 4.15–4.22 (1H, m), 4.24–4.32 (1H, m), 6.49 (1H, s), 6.89 (1H, s), 7.65 (1H, t, J=8.0 Hz), 7.88 (1H, d, J=8.0 Hz), 8.32 (1H, s), 8.37 (1H, d, J=8.0 Hz). (100 MHz, $CDCl_3$): δ 26.8; 51.1; 52.1; 54.3; 56.5; 56.9; 92.1; 110.9; 114.5; 119.9; 123.9; 126.2; 129.4; 133.4; 134.3; 135.1; 147.6; 148.7; 156.9; 164.3; 168.1; 170.3; 171.5. Anal. Calcd for $C_{23}H_{22}N_2O_9$ (470.43) C, 58.72; H, 4.71; N, 5.95; Found C, 58.58; H, 4.80; N, 6.10.

3.5.4. Azomethine ylide 5d. R_f=0.67; yield; Method A, 0.042 g, 91%; Method B, 0.066 g, 71%; dark red crystals; mp 178–179 °C; IR (KBr) $\nu_{C=O}$ 1727; 1665 cm^{-1}. UV/vis λ_{max} $CHCl_3$ nm: 258.0, 262.0, 366.5, 461.5; (400 MHz, $CDCl_3$): δ 3.22–3.29 (2H, m), 3.54 (3H, s), 3.65 (3H, s), 3.71 (3H, s), 4.01 (3H, s), 4.17–4.25 (2H, m), 6.53 (1H, s), 6.86 (1H, s), 7.42 (4H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8; 51.0; 52.1; 54.4; 56.4; 56.9; 96.3; 110.6; 115.1; 120.6; 128.6; 130.1; 130.3; 134.9; 138.1; 148.4; 156.4; 164.3; 168.4; 170.9; 173.7. Anal. Calcd for $C_{23}H_{22}ClNO_7$ (459.88) C, 60.07; H, 4.82; N, 3.05; Found C, 60.15; H, 5.01; N, 3.30.

3.5.5. Azomethine ylide 5e. R_f=0.59; yield; Method A, 0.41 g, 87%; Method B, 0.090 g, 96%; dark red crystals; mp 123–124 °C; IR (KBr) $\nu_{C=O}$ 1734; 1718 cm^{-1}. UV/vis λ_{max} $CHCl_3$ nm: 255.0, 297.5, 386.0; (400 MHz, $CDCl_3$): δ 3.08 (2H, t, J=7.0 Hz), 3.40 (3H, s), 3.70 (3H, s), 3.84 (3H, s), 3.96 (3H, s), 4.08 (2H, t, J=7.0 Hz), 5.98 (2H, s), 6.73 (1H, s), 6.78 (1H, d, J=8.4 Hz), 6.84 (1H, d, J=8.4 Hz), 6.86 (1H, s), 7.40 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.9; 50.9; 52.1; 53.3; 56.43; 56.6; 95.0; 102.1; 105.5; 108.4; 110.2; 115.5; 117.7; 122.2; 132.7; 140.7; 147.3; 148.1; 148.3; 155.0; 167.7; 167.8; 172.5; 180.5. Anal. Calcd for $C_{24}H_{23}NO_9$ (469.44) C, 61.40; H, 4.94; N, 2.98; Found C, 61.50; H, 5.10; N, 3.10.

Acknowledgements

Uludağ University Research Fund and Turkish State Planning Organization (DPT) are gratefully acknowledged for the financial support (Project No 2001-2)

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