An Efficient One-Pot Four-Component Synthesis of Functionalized Imidazo[1,2-*a*]pyridines

by **Siyavash Kazemi Movahed**, **Minoo Dabiri***, and **Ayoob Bazgir**

Department of Chemistry, Shahid Beheshti University, P.O. Box 1983963113, Tehran, Iran
(e-mail: m-dabiri@sbu.ac.ir)

An efficient one-pot four-component protocol for the synthesis of imidazo[1,2-*a*]pyridines was developed by condensing ethane-1,2-diamine (**2**), 1,1-bis(methylthio)-2-nitroethene (**1**), aldehydes **3**, and activated methylene compounds in EtOH under reflux conditions (*Tables 1–3*). The features of this procedure are operational simplicity, good yields of products, *in situ* preparation of heterocyclic ketene aminals (HKA), and catalyst-free conditions.

Introduction. – Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry [1]. They have distinct advantages over a linear stepwise process, including the removal of the need to purify after each chemical transformation, the ability to produce a large number of derivatives around a common scaffold by varying each of the components involved in the reaction, and high atom economy [2].

Heterocyclic ketene aminals (HKAs) are powerful and versatile intermediates in heterocyclic synthesis [3]. Reactions of HKAs with a variety of bis-electrophilic reagents have so far been applied to make five- and six-membered and fused heterocycles during the past years [4]. HKAs have been frequently found as pharmacophores and could play important roles in drug discovery. Recently, *Alizadeh* and co-workers, have reported new MCRs *via in situ* formation of nitroketene aminal for the synthesis of various heterocycles [5]. In this context, imidazo[1,2-*a*]pyridine derivatives show interesting features that make them attractive for use in HKA-based MCRs. HKAs are one of the main intermediates used to synthesize of imidazo[1,2-*a*]pyridines [6].

Imidazo[1,2-*a*]pyridines are becoming more and more important in medicinal and organic chemistry. They have displayed a broad spectrum of pharmacological and biological activities, such as antitumoral [7], antiviral [8], anti-inflammatory [9], antibacterial [10], antifungal [11], anti-ulcer [12], antiprotozoal [13], and antiretroviral activities [14]. They are contained in marketed drugs such as the clinical anti-ulcer compound soraprazan, alpidem (a nonsedative anxiolytic), the PDE 3 inhibitor olprinone, and the sedative zolpidem (*Fig.*) [15]. Bicyclic pyridin motifs **I** are of general interest within medicinal chemistry with therapeutic properties, and a series of substituted variants of **I** ($n = 1$ or 2) have been reported as a basis for analgesics and anti-inflammatory agents (*Fig.*) [16].

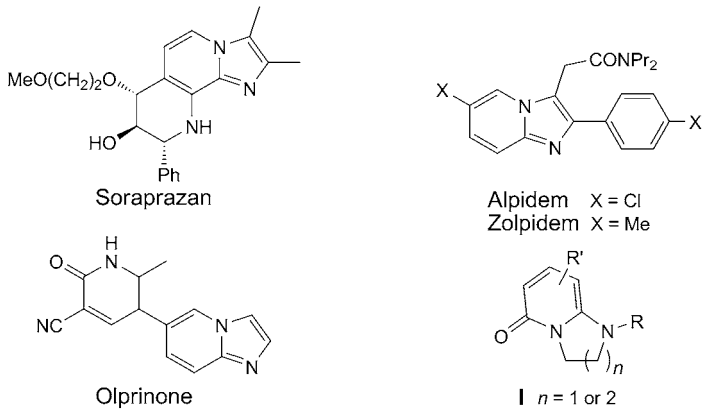
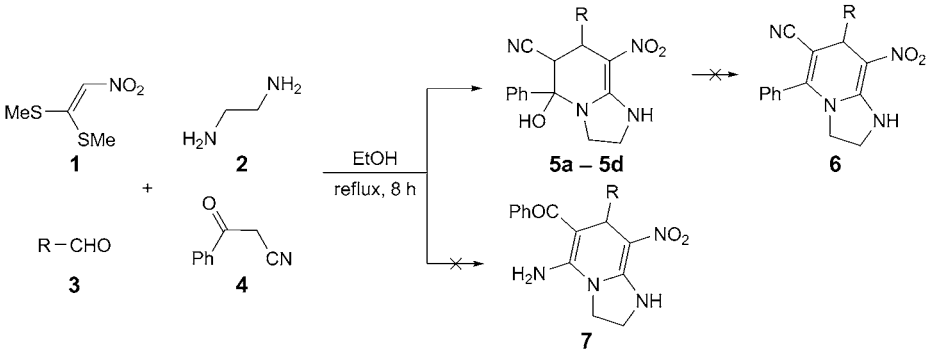


Figure. *Representatives of medicinally important imidazopyridines*

As a part of our current studies on the MCRs to synthesize novel heterocycles [17], we describe herein an efficient four-component synthesis of imidazo[1,2-*a*]pyridines *via in situ* preparation of a nitroketene aminal.

Results and Discussion. – In the initial stage, the reaction of ethane-1,2-diamine (**1**), 1,1-bis(methylthio)-2-nitroethene (**2**), aldehyde **3**, and 3-oxo-3-phenylpropanenitrile (**4**) in EtOH under reflux conditions in the absence of any catalysts led to the formation of imidazo[1,2-*a*]pyridine-6-carbonitriles **5a**–**5d** in good yields after 8 h (*Table 1*). It was interesting that the desired products **6** or **7** were not detected at all. The structures of the products **5a**–**5d** were fully characterized by IR and ^{1}H- and ^{13}C-NMR spectra, and elemental analysis. The ^{1}H-NMR spectrum of **5a** exhibited two *d* at δ(H) 4.27 and

Table 1. *Synthesis of [1,2-*a*]Pyridine-6-carbonitriles* **5**

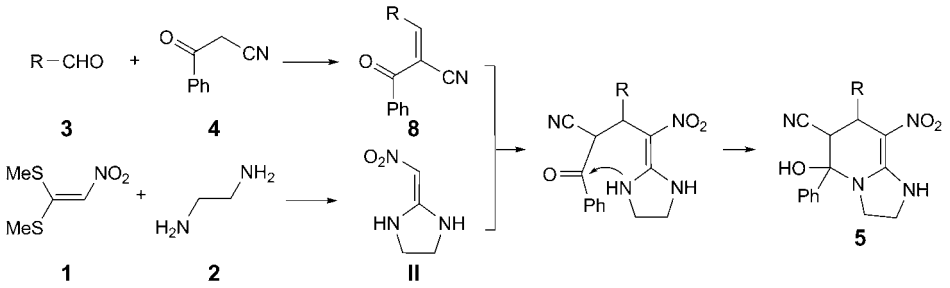


Product **5**	RCHO (**3**)	Yield [%]
5a	Benzaldehyde	61
5b	1*H*-Indole-3-carboxaldehyde	55
5c	4-Fluorobenzaldehyde	85
5d	3-Nitrobenzaldehyde	91

3.52 with $^3J = 11.5$ Hz for the CH groups that confirmed non-dehydration of product **5** and indicated *trans*-configuration of the two vicinal H-atoms.

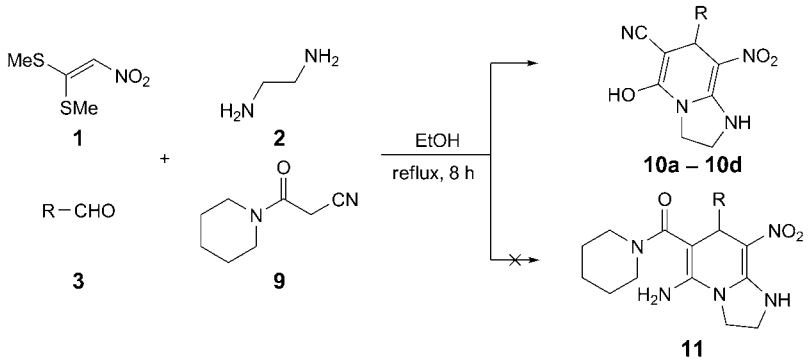
The formation of products **5** can be rationalized by the initial formation of intermediate **8** *via Knoevenagel* condensation of **3** and **4**. Subsequent addition of HKA **II** (formed *in situ* by reaction of **1** with **2**) to the intermediate **8** followed by cyclization afforded products **5** (*Scheme*).

Scheme. *Proposed Mechanism of the Formation of Product* **5**



To further explore the potential of this protocol for the imidazo[1,2-*a*]pyridine synthesis, the 3-oxo-3-(piperidin-1-yl)propanenitrile (**9**) was selected as an activated-methylene compound in the four-component reaction (*Table 2*). It was interesting that the 5-aminoimidazo[1,2-*a*]pyridin **11** was not detected at all, while imidazo[1,2-*a*]pyridines **10** were obtained in good yields. All the products were characterized by IR, mass, and NMR spectra and elemental analysis.

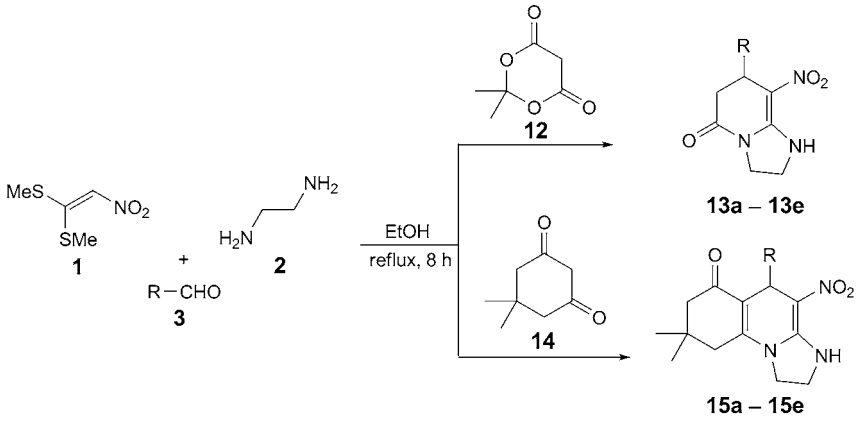
Table 2. *Synthesis of Imidazo[1,2-*a*]pyridines* **10**



Product **10**	RCHO (**3**)	Yield [%]
10a	Benzaldehyde	65
10b	3-Nitrobenzaldehyde	83
10c	Pyridine-2-carboxaldeyde	79
10d	2-Nitrobenzaldehyde	75

When *Meldrum*'s acid (**12**) and dimedone (**14**) were selected as active β-dicarbonyl compounds in the four-component reaction, the desired imidazo[1,2-*a*]pyridines **13** and **15** were obtained in good yields (*Table 3*).

Table 3. *Synthesis of Compounds* **13** *and* **15**



Product	RCHO (**3**)	Yield [%]
13a	Benzaldehyde	57
13b	2,4-Dichlorobenzaldehyde	71
13c	3-Nitrobenzaldehyde	74
13d	4-Methoxybenzaldehyde	67
13e	Pyridine-2-carboxaldeyde	70
15a	Benzaldehyde	51
15b	Pyridine-2-carboxaldeyde	68
15c	1*H*-Indole-3-carboxaldehyde	45
15d	3-Nitrobenzaldehyde	83
15e	4-Methoxybenzaldehyde	54

In conclusion, we achieved the new one-pot, four-component, and catalyst-free synthesis of highly functionalized imidazo[1,2-*a*]pyridines. The catalyst-free reactions carried out in EtOH are considerably safer, nontoxic, environmentally friendly, and inexpensive. The absence of a catalyst for the reaction avoids the use of moisture sensitive and heavy metal such as *Lewis* acids. This method is applicable to the synthesis of different types of imidazo[1,2-*a*]pyridines.

We gratefully acknowledge financial support from the *Research Council of Shahid Beheshti University.*

Experimental Part

General. The chemicals used in this work were obtained from *Fluka* and *Merck* and were applied without further purification. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *BOMEM-MB-series* FT-IR apparatus; $\tilde{\nu}$ in cm^{-1}. ^1H-and ^{13}C- Spectra: *Bruker-DRX-300-Avance* spectrometer; at 300.13 and 75.47 MHz, resp.; in (D_6)DMSO; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS

(70 eV): *Shimadzu-GCMS-QP1100EX* mass spectrometer; in *m/z*. *VarioEL-CHNS* apparatus Elemental analyses: (*Elementar Analysensysteme GmbH)*.

Compounds **5a**–**5d**. *General Procedure.* A soln. of ethane-1,2-diamine (**1**; 1 mmol) and 1,1-bis(methylthio)-2-nitroethene (**2**; 1 mmol) in EtOH (5 ml) was magnetically stirred for 3 h under reflux. Then a soln. of aldehyde **3** (1 mmol) and 3-oxo-3-phenylpropanenitrile (**4**; 1 mmol) in EtOH (3 ml) was added to the mixture and refluxed for 5 h. The mixture was cooled to r.t. and the precipitated product collected by filtration and washed with AcOEt (2 × 3 ml): **5**.

*1,2,3,5,6,7-Hexahydro-5-hydroxy-8-nitro-5,7-diphenylimidazo[1,2-*a*]pyridine-6-carbonitrile* (**5a**): Yield 61%. White solid. M.p. 205–208°. IR (KBr): 3362, 2903, 2251, 1601. ^{1}H-NMR: 3.29–3.39 (*m*, CH_2); 3.52 (*d*, *J* = 11.5, CH); 3.62–3.64 (*m*, CH_2), 4.26 (*d*, *J* = 11.5, CH); 7.20–7.67 (*m*, 10 arom. H); 9.35 (br. *s*, NH). ^{13}C-NMR: 42.8; 43.1; 45.1; 50.5; 83.7; 105.8; 118.2; 126.9; 127.1; 127.9; 128.6; 129.4; 139.3; 141.7; 157.4. MS: 362 (M^+). Anal. calc. for $C_{20}H_{18}N_4O_3$ (362.38): C 66.29, H 5.01, N 15.46; found: C 66.32, H 5.06, N 15.43.

*1,2,3,5,6,7-Hexahydro-5-hydroxy-7-(1*H*-indol-3-yl)-8-nitro-5-phenylimidazo[1,2-*a*]pyridine-6-carbonitrile* (**5b**): Yield 55%. White solid. M.p. 198–200°. IR (KBr): 3333, 2923, 2251, 1620. ^{1}H-NMR: 3.40–3.47 (*m*, CH_2); 3.52–3.62 (*m*, CH_2); 4.46 (*d*, *J* = 6.9, CH); 4.83 (*d*, *J* = 6.9, CH); 7.41–7.95 (*m*, 9 arom. H); 8.57 (*s*, 1 arom. H); 9.38 (br. *s*, NH); 10.11 (br. *s*, NH). ^{13}C-NMR: 19.0; 42.5; 44.3; 56.5; 82.9; 105.0; 117.1; 123.8; 127.1; 127.2; 127.4; 129.0; 129.4; 138.5; 139.9; 147.9; 155.7; 157.5. MS: 401 (M^+). Anal. calc. for $C_{22}H_{19}N_5O_3$ (401.42): C 66.83, H 4.77, N 17.45; found: C 66.80, H 4.71, N 17.45.

*7-(4-Fluorophenyl)-1,2,3,5,6,7-hexahydro-5-hydroxy-8-nitro-5-phenylimidazo[1,2-*a*]pyridine-6-carbonitrile* (**5c**): Yield 85%. White solid. M.p. 209–212°. IR (KBr): 3283, 2879, 2257, 1617. ^{1}H-NMR: 3.32–3.35 (*m*, CH_2); 3.54–3.63 (*m*, CH, CH_2); 4.26 (*d*, *J* = 11.4, CH); 7.05–7.65 (*m*, 9 arom. H); 9.34 (br. *s*, NH). ^{13}C-NMR: 42.0; 43.1; 45.5; 50.1; 83.6; 105.6; 115.0; 118.1; 127.3; 128.9; 129.4; 129.8; 129.9; 139.2; 139.9; 157.3. MS: 380 (M^+). Anal. calc. for $C_{20}H_{17}FN_4O_3$ (380.37): C 63.15, H 4.50, N 14.73; found: C 63.20, H 4.52, N 14.71.

*1,2,3,5,6,7-Hexahydro-5-hydroxy-8-nitro-7-(3-nitrophenyl)-5-phenylimidazo[1,2-*a*]pyridine-6-carbonitrile* (**5d**): Yield 91%. White solid. M.p. 224–256°. IR (KBr): 3300, 3097, 2965, 2905, 2247, 1613. ^{1}H-NMR: 3.12–3.20 (*m*, CH_2); 3.66–3.88 (*m*, CH, CH_2); 4.24–4.47 (*d*, *J* = 11.3, CH); 6.79–7.04 (*m*, 9 arom. H); 9.37 (br. *s*, NH). ^{13}C-NMR: 43.0; 43.8; 55.4; 83.6; 104.8; 117.9; 122.2; 127.2; 127.3; 128.9; 129.5; 129.9; 135.6; 139.1; 139.8; 143.8; 157.3. MS: 407 (M^+). Anal. calc. for $C_{20}H_{17}N_5O_5$ (407.38): C 58.97, H 4.21, N 17.19; found: C 59.02, H 4.25, N 17.15.

Compounds **10a**–**10d**. *General Procedure.* As described for **5a**–**5d**, with ethane-1,2-diamine (**1**; 1 mmol), l,l-bis(methylthio)-2-nitroethene (**2**; 1 mmol), EtOH (5 ml), aldehyde **3** (1 mmol), and 3-oxo-3-(piperidin-1-yl)propanenitrile (**9**; 1 mmol) in EtOH (3 ml): **10**.

*1,2,3,7-Tetrahydro-5-hydroxy-8-nitro-7-phenylimidazo[1,2-*a*]pyridine-6-carbonitrile* (**10a**): Yield 65%. Yellow solid. M.p. 260–265° (dec.). IR (KBr): 3395, 3288, 2887, 1641, 1614. ^{1}H-NMR: 3.68–3.74 (*m*, CH_2); 3.88–3.94 (*m*, CH_2); 4.97 (*s*, CH); 7.08–7.17 (*m*, 3 arom. H); 7.28–7.30 (*m*, 2 arom. H); 8.30 (br. *s*, OH); 9.21 (br. *s*, NH). ^{13}C-NMR: 43.2; 43.5; 43.8; 74.7; 108.3; 126.2; 127.7; 128.1; 146.4; 153.8; 162.6. MS: 284 (M^+). Anal. calc. for $C_{14}H_{12}N_4O_3$ (284.27): C 59.15, H 4.25, N 19.71; found: C 59.19, H 4.20, N 19.75.

*1,2,3,7-Tetrahydro-5-hydroxy-8-nitro-7-(3-nitrophenyl)imidazo[1,2-*a*]pyridine-6-carbonitrile* (**10b**). Yield 83%. Yellow solid. M.p. 256–258° (dec.). IR (KBr): 3340, 3321, 2879, 1640, 1638. ^{1}H-NMR: 3.73–3.81 (*m*, CH_2); 3.90–3.97 (*m*, CH_2); 5.15 (*s*, CH); 7.30 (*s*, 1 arom. H); 7.47–7.52 (*m*, 1 arom. H); 7.71–7.64 (*m*, 1 arom. H); 7.97–7.99 (*m*, 1 arom. H); 8.36 (br. *s*, OH); 9.16 (br. *s*, NH). ^{13}C-NMR: 43.2; 43.5; 43.8; 73.8; 107.4; 121.5; 122.5; 129.7; 134.5; 147.5; 148.5; 153.6; 152.4; 162.8. MS: 329 (M^+). Anal. calc. for $C_{14}H_{11}N_5O_5$ (329.27): C 51.07, H 3.37, N 21.27; found: C 51.19, H 3.20, N 21.21.

*1,2,3,7-Tetrahydro-5-hydroxy-8-nitro-7-(pyridin-2-yl)imidazo[1,2-*a*]pyridine-6-carbonitrile* (**10c**). Yield 79%. Yellow solid. M.p. 264–268° (dec.). IR (KBr): 3385, 3288, 2885, 1643, 1630. ^{1}H-NMR: 3.73–3.92 (*m*, 2 CH_2); 5.03 (*s*, CH); 7.13 (*s*, 1 arom. H); 7.26–7.28 (*m*, 1 arom. H); 7.45 (*s*, 1 arom. H); 7.60–7.63 (*m*, 1 arom. H); 8.36 (br. *s*, OH), 9.28 (br. *s*, NH). ^{13}C-NMR: 43.2; 43.5; 43.9; 73.8; 106.3; 121.3; 121.8; 136.9; 148.9; 154.1; 162.1; 163.3; 164.4. MS: 285 (M^+). Anal. calc. for $C_{13}H_{11}N_5O_3$ (285.26): C 54.74, H 3.89, N 24.55; found: C 34.75, H 3.89, N 24.56.

*1,2,3,7-Tetrahydro-5-hydroxy-8-nitro-7-(2-nitrophenyl)imidazo[1,2-*a*]pyridine-6-carbonitrile* (**10d**). Yield 75%. Yellow solid. M.p. 236–238°. IR (KBr): 3517, 3391, 2941, 2864, 1644, 1530. ^{1}H-NMR: 3.61–3.66 (*m*, CH_2); 4.11–4.14 (*m*, CH_2); 4.74 (*s*, CH); 7.21–7.23 (*m*, 1 arom. H); 7.50–7.53 (*m*, 1 arom. H); 7.61–7.64 (*m*, 1 arom. H); 7.93–7.95 (*m*, 1 arom. H); 8.75 (br. *s*, OH), 9.59 (br. *s*, NH). ^{13}C-NMR: 43.3; 43.6; 45.1; 74.6; 106.3; 124.8; 128.8; 128.9; 134.3; 136.8; 149.3; 166.4. MS: 329 (M^+). Anal. calc. for $C_{14}H_{11}N_5O_5$ (329.27): C 51.07, H 3.37, N 21.27; found: C 51.10, H 3.39, N 21.25.

Compounds **13a**–**13e**. *General Procedure.* As described for **5a**–**5d**, with ethane-1,2-diamine (**1**; 1 mmol) 1,1-bis(methylthio)-2-nitroethene (**2**; 1 mmol), EtOH (5 ml), aldehyde **3** (1 mmol), and *Meldrum*'s acid (=2,2-dimethyl-1,3-dioxane-4,6-dione; **12**; 1 mmol) in EtOH (3 ml): **13**.

*2,3,6,7-Tetrahydro-8-nitro-7-phenylimidazo[1,2-*a*]pyridin-5(1*H*)-one* (**13a**). Yield 57%. White solid. M.p. 252–256°. IR (KBr): 3224, 3007, 2917, 1699. ^{1}H-NMR: 2.55–2.60 (*m*, CH); 3.16–3.24 (*m*, CH); 3.75–3.97 (*m*, 2 CH_2); 4.52–4.55 (*m*, CH); 7.13–7.18 (*m*, 2 arom. H); 7.20–7.32 (*m*, 3 arom. H); 9.71 (br. *s*, NH). ^{13}C-NMR: 37.6; 40.6; 43.05; 43.9; 106.7; 126.8; 127.3; 129.1; 142.9; 153.1; 167.8. MS: 259 (M^+). Anal. calc. for $C_{13}H_{13}N_3O_3$ (259.26): C 60.22, H 5.05, N 16.21; found: C 60.25, H 5.08, N 16.13.

*7-(2,4-Dichlorophenyl)-2,3,6,7-tetrahydro-8-nitroimidazo[1,2-*a*]pyridin-5(1*H*)-one* (**13b**): Yield 71%. White solid. M.p. 246–247°. IR (KBr): 3294, 3073, 2923, 1709. ^{1}H-NMR: 2.46–2.50 (*m*, CH); 3.25–3.31 (*m*, CH); 3.81–3.91 (*m*, 2 CH_2); 4.83–4.86 (*m*, CH); 7.10 (*d*, J = 8.18, 1 arom. H); 7.30 (*d*, J = 8.18, 1 arom. H); 7.64 (*s*, 1 arom. H); 9.82 (br. *s*, NH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 35.5; 37.7; 43.2; 44.1; 104.9; 128.2; 128.7; 129.8; 132.8; 133.8; 138.8; 153.4; 166.9. MS: 328 (M^+). Anal. calc. for $C_{13}H_{11}Cl_2N_3O_3$ (328.15): C 47.58, H 3.38, N 12.81; found: C 47.60, H 3.31, N 12.85.

*2,3,6,7-Tetrahydro-8-Nitro-7-(3-nitrophenyl)imidazo[1,2-*a*]pyridin-5(1*H*)-one* (**13c**). Yield 74%. White solid. M.p. 236–240°. IR (KBr): 3378, 3058, 2917, 1713. ^{1}H-NMR: 2.64–2.69 (*m*, CH); 3.22–3.30 (*m*, CH); 3.79–3.93 (*m*, 2 CH_2); 4.70–4.73 (*m*, CH); 7.58–7.60 (*m*, 2 arom. H); 8.01–8.04 (*m*, 1 arom. H); 8.06 (*s*, 1 arom. H); 9.75 (br. *s*, NH). ^{13}C-NMR: 37.3; 37.7, 39.9; 44.0; 105.9; 121.9; 122.4; 130.7; 133.4; 145.2; 148.4; 153.1; 167.4. MS: 304 (M^+). Anal. calc. for $C_{13}H_{12}N_4O_5$ (304.26): C 51.32, H 3.98, N 18.41; found: C 51.36, H 4.02, N 18.40.

*2,3,6,7-Tetrahydro-7-(4-methoxyphenyl)-8-nitroimidazo[1,2-*a*]pyridin-5(1*H*)-one* (**13d**): Yield 67%. White solid. M.p. 237–241° (dec.). IR (KBr): 3224, 3000, 2911, 1699. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.55–2.57 (*m*, CH); 3.11–3.17 (*m*, CH); 3.68 (*s*, Me); 3.77–3.92 (*m*, 2 CH_2); 4.45–4.47 (*m*, CH); 6.82 (*d*, J = 6.4, 2 arom. H); 7.04 (*d*, J = 6.4, 2 arom. H); 9.75 (br. *s*, NH). ^{13}C-NMR: 36.7; 43.0; 43.9; 55.5; 107.0; 114.4; 127.8; 134.7; 153.0; 158.2; 167.9. MS: 289 (M^+). Anal. calc. for $C_{14}H_{15}N_3O_4$ (289.29): C 58.13, H 5.23, N 14.53; found: C 58.15, H 5.25, N 14.55.

*2,3,6,7-Tetrahydro-8-nitro-7-(pyridin-2-yl)imidazo[1,2-*a*]pyridin-5(1*H*)-one* (**13e**). Yield 70%. White solid. M.p. 242–244°. IR (KBr): 3204, 3013, 2930, 1699, 1636, 1588. ^{1}H-NMR: 2.63–2.69 (*m*, CH); 3.08–3.13 (*m*, CH); 3.77–3.94 (*m*, 2 CH_2); 4.44–4.46 (*m*, CH); 7.21–7.29 (*m*, 2 arom. H); 7.68–7.70 (*m*, 1 arom. H); 8.39–8.41 (*m*, 1 arom. H); 9.64 (br. *s*, NH). ^{13}C-NMR: 37.2; 42.9; 43.7; 106.5; 122.4; 122.8; 137.2; 149.7; 153.3; 161.5; 167.9. MS: 260 (M^+). Anal. calc. for $C_{12}H_{12}N_4O_3$ (260.25): C 55.38, H 4.65, N 21.53; found: C 55.40, H 4.68, N 21.50.

Compounds **15a**–**15e**. *General Procedure.* As described for **5a**–**5d**, with ethane-1,2-diamine (**1**; 1 mmol), and 1,1-bis(methylthio)-2-nitroethene (**2**; 1 mmol), EtOH (5 ml), aldehyde **3** (1 mmol), and dimedone (=5,5-dimethylcyclohexane-1,3-dione; **14**, 1 mmol) in EtOH (3 ml): **15**.

*2,3,5,7,8,9-Hexahydro-8,8-dimethyl-4-nitro-5-phenylimidazo[1,2-*a*]quinolin-6(1*H*)-one* (**15a**): Yield 51%. Yellow solid. M.p. 264–267°. IR (KBr): 3338, 2960, 2929, 2863, 1722, 1637. ^{1}H-NMR: 0.83 (*s*, Me); 1.03 (*s*, Me); 2.08 (*ABq*, J = 15.5, CH_2); 2.49–2.57 (*m*, CH_2); 3.56–3.82 (*m*, CH_2); 4.06 (*m*, CH_2); 5.07 (*s*, CH); 7.09–7.20 (*m*, 5 arom. H); 9.41 (br. *s*, NH). ^{13}C-NMR: 26.5; 29.8; 32.2; 38.7; 43.8; 45.2; 49.9; 107.8; 114.1; 126.5; 128.1; 128.3; 144.7; 149.5; 152.1; 193.7. MS: 339 (M^+). Anal. calc. for $C_{19}H_{21}N_3O_3$ (339.39): C 67.24, H 6.26, N 12.38; found: C 67.20, H 6.29, N 12.35.

*2,3,5,7,8,9-Hexahydro-8,8-dimethyl-4-nitro-5-(pyridin-2-yl)imidazo[1,2-*a*]quinolin-6(1*H*)-one* (**15b**): Yield 68%. Yellow solid. M.p. 280–285° (dec.). IR (KBr): 3340, 2949, 2901, 1667. ^{1}H-NMR: 0.78 (*s*, Me); 1.01 (*s*, Me); 2.06 (*ABq*, J = 15.9, CH_2); 2.42–2.59 (*m*, CH_2); 3.80–3.86 (*m*, CH_2); 3.98–4.15 (*m*, CH_2); 5.07 (*s*, CH); 7.06–7.09 (*m*, 1 arom. H); 7.37–7.39 (*m*, 1 arom. H); 7.57–7.61 (*m*, 1 arom. H); 8.30–8.33 (*m*, 1 arom. H); 9.44 (br. *s*, NH). ^{13}C-NMR: 26.2; 29.9; 32.2; 38.7; 40.3; 43.7; 45.1; 49.8; 107.3; 113.1; 121.9;

124.5; 135.7; 149.2; 150.1; 152.5; 162.15; 193.8. MS: 340 (M^+). Anal. calc. for $C_{18}H_{20}N_4O_3$ (340.38): C 63.52, H 5.92, N 16.46; found: C 63.56, H 5.95, N 16.47.

*2,3,5,7,8,9-Hexahydro-5-(1*H*-indol-3-yl)-8,8-dimethyl-4-nitro-imidazo[1,2-*a*]quinolin-6(1*H*)-one* (**15c**): Yield 45%. Yellow solid. M.p. 275–277° (dec.). IR (KBr): 3359, 3321, 2955, 2879, 1655. ^{1}H-NMR: 0.77 (*s*, Me); 1.01 (*s*, Me); 2.05 (*ABq*, $J = 15.8$, CH_2); 2.51–2.59 (*m*, CH_2); 3.80–3.87 (*m*, CH_2); 4.02–4.21 (*m*, CH_2); 5.04 (*s*, CH); 6.90–7.96 (*m*, 5 arom. H); 9.32 (br. *s*, NH); 10.76 (br. *s*, NH). ^{13}C-NMR: 26.6; 29.1; 29.9; 32.1; 38.6; 43.8; 45.3; 49.9; 107.9; 111.6; 114.3; 117.8; 118.7; 119.7; 120.7; 124.0; 126.2; 136.4; 148.5; 152.1; 193.8. MS: 378 (M^+). Anal. calc. for $C_{21}H_{22}N_4O_3$ (378.42): C 66.65, H 5.86, N 14.81; found: C 66.60, H 5.85, N 14.80.

*2,3,5,7,8,9-Hexahydro-8,8-dimethyl-4-nitro-5-(3-nitrophenyl)-imidazo[1,2-*a*]quinolin-6(1*H*)-one* (**15d**). Yield 83%. Yellow solid. M.p. 285–287° (dec.). IR (KBr): 3359, 3071, 2943, 2935, 1661. ^{1}H-NMR: 0.83 (*s*, Me); 1.04 (*s*, Me); 2.08 (*ABq*, $J = 16.0$, CH_2); 2.56–2.65 (*m*, CH_2); 3.82–3.88 (*m*, CH_2); 3.98–4.23 (*m*, CH_2); 5.14 (*s*, CH); 7.48–7.54 (*m*, 1 arom. H); 7.68–7.70 (*m*, 1 arom. H); 7.98–8.04 (*m*, 2 arom. H); 9.5 (br. *s*, NH). ^{13}C-NMR: 26.4; 29.8; 32.3; 38.2; 38.7; 43.9; 45.3; 49.6; 107.0; 112.8; 121.7; 123.0; 129.7; 135.0; 146.9; 147.6; 150.3; 151.8; 193.8. MS: 384 (M^+). Anal. calc. for $C_{19}H_{20}N_4O_5$ (384.39): C 59.37, H 5.24, N 14.58; found: C 59.30, H 5.29, N 14.52.

*2,3,5,7,8,9-Hexahydro-5-(4-methoxyphenyl)-8,8-dimethyl-4-nitro-imidazo[1,2-*a*]quinolin-6(1*H*)-one* (**15e**): Yield 54%. Yellow solid. M.p. 286–289° (dec.). IR (KBr): 3346, 3007, 2962, 2898, 1656. ^{1}H-NMR: 0.85 (*s*, Me); 1.04 (*s*, Me); 2.08 (*ABq*, $J = 16.0$, CH_2); 2.45–2.61 (*m*, CH_2); 3.67 (*s*, Me); 3.82–3.86 (*m*, CH_2); 3.98–4.18 (*m*, CH_2); 5.03 (*s*, CH); 6.73 (*d*, $J = 7.8$, 2 arom. H); 7.11 (*d*, $J = 7.4$, 2 arom. H); 9.33 (br. *s*, NH). ^{13}C-NMR: 26.5; 29.9; 32.2; 38.7; 38.6; 43.8; 45.2; 49.9; 55.3; 108.0; 113.4; 114.4; 129.2; 136.9; 149.1; 152.0; 157.9; 193.7. MS: 369 (M^+). Anal. calc. for $C_{20}H_{23}N_3O_4$ (369.41): C 65.03, H 6.28, N 11.37; found: C 65.08, H 6.30, N 11.35.

REFERENCES

[1] I. Ugi, A. Dömling, W. Hörl, *Endeavour* **1994**, *18*, 115; R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123; L. F. Tietze, M. E. Lieb, *Curr. Opin. Chem. Biol.* **1998**, *2*, 363; S. L. Dax, J. J. McNally, M. A. Youngman, *Curr. Med. Chem.* **1999**, *6*, 255; C. O. Kappe, *Acc. Chem. Res.* **2000**, *33*, 879.

[2] H. Eckert, *Heterocycles* **2007**, *73*, 149; C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51; L. Weber, *Curr. Med. Chem.* **2002**, *9*, 2085; L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 366.

[3] S.-J. Yan, C. Huang, C.-X. Su, Y.-F. Ni, J. Lin, *J. Comb. Chem.* **2010**, *12*, 91; S.-J. Yan, C. Huang, X.-H. Zeng, R. Huang, J. Lin, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 48; S.-J. Yan, Y.-F. Niu, R. Huang, J. Lin, *Synlett* **2009**, 2821.

[4] L.-R. Wen, C.-Y. Jiang, M. Li, L.-J. Wang, *Tetrahedron* **2011**, *67*, 293 and ref. cit. therein

[5] A. Alizadeh, A. Rezvanian, *Synlett* **2011**, 1105; A. Alizadeh, A. Rezvanian, D. Yuan, *Tetrahedron* **2010**, *66*, 9933; A. Alizadeh, A. Rezvanian, *Helv. Chim. Acta.* **2012**, *95*, 152.

[6] S.-J. Yan, Y.-L. Chen, L. Liu, N.-Q. He, J. Lin, *Green Chem.* **2010**, *12*, 2043; M. Li, Z.-M. Zhou, L.-R. Wen, Z.-X. Qiu, *J. Org. Chem.* **2011**, *76*, 3054; Z.-H. Xu, Y.-F. Jie, M.-X. Wang, Z.-T. Huang, *Synthesis* **2002**, 523; M.-X. Wang, W.-S. Miao, Y. Cheng, Z.-T. Huang, *Tetrahedron* **1999**, *55*, 14611; S. Chakrabarti, K. Panda, N. C. Misra, H. Ila, H. Junjappa, *Synlett* **2005**, 1437; C.-Y. Yu, P.-H. Yang, M.-X. Zhao, Z.-T. Huang, *Synlett* **2006**, 1835; J.-P. Liao, T. Zhang, C.-Y. Yu, Z.-T. Huang, *Synlett* **2007**, 761; M. Yaqub, C.-Y. Yu, Y.-M. Jia, Z.-T. Huang, *Synlett* **2008**, 1357.

[7] A. Kamal, J. S. Reddy, M. J. Ramaiah, D. Dastagiri, E. V. Bharathi, M. V. P. Sagar, S. N. C. V. L. Pushpavalli, P. Ray, M. Pal-Bhadra, *Med. Chem. Commun.* **2010**, *1*, 355; M. A. Martinez-Urbina, A. Zentella, M. A. Vilchis-Reyes, A. Guzman, O. Vargas, M. T. Ramirez Apan, J. L. Ventura Gallegos, E. Diaz, *Eur. J. Med. Chem.* **2010**, *45*, 1211; M. A. Vilchis-Reyes, A. Zentella, M. A. Martinez-Urbina, A. Guzman, O. Vargas, M. T. Ramirez Apan, J. L. Ventura Gallegos, E. Diaz, *Eur. J. Med. Chem.* **2010**, *45*, 379.

[8] A. Gueiffier, M. Lhassani, A. Elhakmaoui, R. Snoeck, G. Andrei, O. Chavignon, J.-C. Teulade, A. Kerbal, E. M. Essassi, J.-C. Debouzy, M. Witvrouw, Y. Blache, J. Balzarini, E. De Clercq, J.-P.

Chapat, *J. Med. Chem.* **1996**, *39*, 2856; J.-M. Chezal, J. Paeshuyse, V. Gaumet, D. Canitrot, A. Maisonial, C. Lartigue, A. Gueiffier, E. Moreau, J.-C. Teulade, O. Chavignon, J. Neyts, *Eur. J. Med. Chem.* **2010**, *45*, 2044; S. Mavel, J.-L. Renou, C. Galtier, H. Allouchi, R. Snoeck, G. Andrei, E. De Clercq, J. Balzarini, A. Gueiffiera, *Bioorg. Med. Chem.* **2002**, *10*, 941.

[9] A. D. Chiacchio, M. G. Rimoli, L. Avallonea, F. Arena, E. Abignente, W. Filippelli, A. Filippelli, G. Falcone, *Arch. Pharm*. **1998**, *331*, 273; A. K. Saxena, K.-J. Schaper, *QSAR Comb. Sci.* **2006**, *25*, 590.

[10] P. J. Beswick, I. B. Campbell, A. Naylor, to *Glaxo Group Ltd.,* WO 9631509, 10.10.1996 (*Chem. Abstr.* **1997**, *126*, 8117j).

[11] A. Ozdemir, G. Turan-Zitouni, Z. Asim Kaplancikli, G. Iscan, S. Khan, F. Demirci, *Eur. J. Med. Chem.* **2010**, *45*, 2080.

[12] J. J. Kaminski, A. M. Doweyko, *J. Med. Chem.* **1997**, *40*, 427.

[13] M. A. Ismail, R. Brun, T. Wenzler, F. A. Tanious, W. D. Wilson, D. W. Boykin, *J. Med. Chem.* **2004**, *47*, 3658; M. Bollini, J. J. Casal, D. E. Alvarez, L. Boiani, M. Gonzalez, H. Cerecetto, A. M. Bruno, *Bioorg. Med. Chem.* **2009**, *17*, 1437; W.-W. Zhang, Y.-B. Chen, W.-D. Chen, Z.-W. Liu, Z. Li, *J. Agric. Food Chem.* **2010**, *58*, 6296.

[14] A. Chaouni-Benabdallah, C. Galtier, H. Allouchi, A. Kherbeche, J. C. Debouzy, J. C. Teulade, O. Chavignon, M. Witvrouw, C. Pannecouque, J. Balzarini, E. De Clercq, C. Enguehard, A. Gueiffier, *Arch. Pharm.* **2001**, *334*, 224.

[15] S. Z. Langer, S. Arbilla, J. Benavides, B. Scatton, *Adv. Biochem. Psychopharmacol*. **1990**, *46*, 61; T. Ueda, K. Mizusgige, K. Yukiiri, T. Takahashi, M. Kohno, *Cerebrovasc. Dis.* **2003**, *16*, 396; T. S. Harrison, G. M. Keating, *CNS Drugs* **2005**, *19*, 65.

[16] K. Kazuo, I. Noriki, S. Isao, I. Yasuo, H. Hiroshige, M. Masuo, to *Yamanouchi Pharmaceutical Co., Ltd.*, Tokyo, U.S. Pat. 4 186 200, 29.01.1980; M. J. Frohn, F.-T. Hong, L. Liu, P. Lopez, A. C. Siegmund, S. Tadesse, N. Tamayo, to *Amgen Inc.*, WO 2005070932, 04.08.2005; C. Alonso-Alija, M. Michels, H. Schirok, K.-H. Schlemmer, S. Dodd, M. Fitzgerald, J. Bell, A. Gill, to *Bayer AG*, WO 03053967, 03.07.2003; D. Cheng, L. Croft, M. Abdi, A. Lightfoot, T. Gallagher, *Org. Lett.* **2007**, *9*, 5175.

[17] P. Salehi, M. Dabiri, M. Koohshari, S. K. Movahed, M. Bararjanian, *Mol. Diversity* **2011**, *15*, 833; G. I. Shakibaei, A. Feiz, H. R. Khavasi, A. A. Soorki, A. Bazgir, *ACS Comb. Sci.* **2011**, *13*, 96; R. Akbarzadeh, T. Amanpour, A. A. Soorki, A. Bazgir, *Helv. Chim. Acta* **2012**, *95*, 483; S. Ahadi, L. Moafi, A. Feiz, A. Bazgir, *Tetrahedron* **2011**, *67*, 3954; L. Torkian, M. Dabiri, P. Salehi, M. Bararjanian, *Helv. Chim. Acta* **2011**, *94*, 1416; M. Dabiri, Z. N. Tisseh, A. Bazgir, *Dyes Pigments* **2011**, *89*, 63.

Received May 5, 2012