One-pot Synthesis of Benzo[4,5]imidazo[1,2-*a*]pyridine Derivatives in Aqueous Conditions

Maria A. Vodolazhenko,[a] Anastasiia E. Mykhailenko,[a] Nikolay Yu. Gorobets,[a]* and Sergey M. Desenko[a,b]

[a]Department of Chemistry of Heterocyclic Compounds, SSI "Institute for Single Crystals" of National Academy of Sciences of Ukraine, Nauky Avenue 60, Kharkiv 61001, Ukraine
[b]Faculty of Chemistry, V.N. Karazin Kharkiv National University, Svobody Sq. 4, Kharkiv 61077, Ukraine
*E-mail: gorobets@isc.kharkov.com

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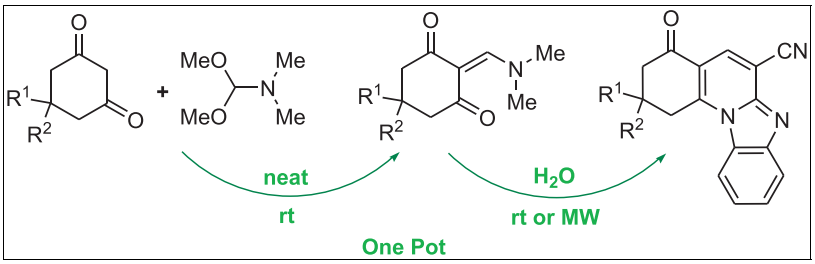


One-pot reaction of cyclic 1,3-diketones, dimethylformamide dimethylacetal (DMFDMA) and 2-(1*H*-benzo[*d*]imidaz-2-yl)acetonitrile was found to be a highly selective process leading to 4-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]quinolin-6-yl cyanides. Optimized reaction conditions using water as solvent at room temperature or under microwave heating allowed high yields of the target products required no additional purification.

INTRODUCTION

The concept of green chemistry is widely applied today not only in the industrial scale of organic chemistry but also in the research and educational laboratories to instill this chemical philosophy and to expand the boundaries of the classical methods of organic chemistry [1]. The limited solubility of organic reactants in water used to be considered as the main disadvantage of this media. However, a great variety of chemical process in living organisms and in nature proceeds in water medium. Water as solvent has advantages over organic solvents because it meets several green chemistry principles, being nontoxic, nonflammable, odorless, and available at low cost; also, "organic-free" water can be recovered for further use. Moreover, for reactions "on water," the limited solubility of starting compounds favors the process, and for reactions "in water," where starting materials are soluble, the isolation and purification of the product are often facilitated because of their low solubility in the aqueous media [2]. That is why organic reactions in aqueous media attract more and more attention [3–8].

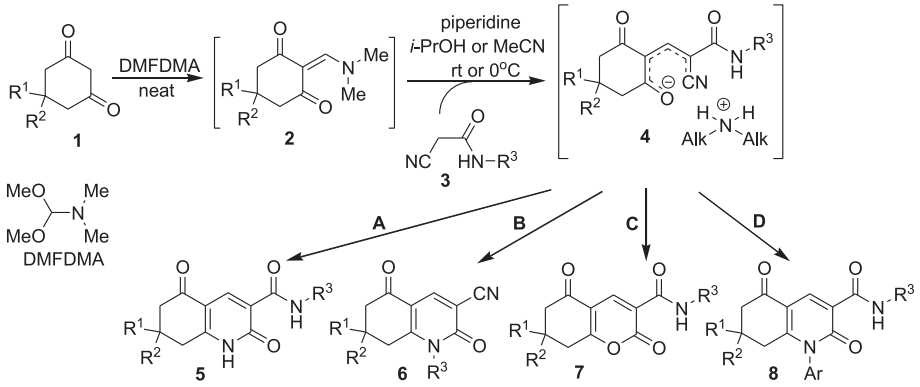
Our research during last years was devoted to elaboration of selectivity control methods for the synthesis of different heterocycles based on one-pot reaction of α-CH_2-carbonyl compounds, dimethylformamide dimethylacetal (DMFDMA), and active methylene nitrile compounds [9–15]. In particular, we have shown that this interaction using cyclic 1,6-dicarbonyl compounds **1** and cyanoacetamides **3** have different outcome [9–11] depending on reaction conditions (ways **A–C**, Scheme 1). Moreover, the isolation of the polyfunctional intermediate enolates **4** allows their other transformations [12–14], for example, with aromatic amines (way **D**). This enolates are readily soluble in water, and as one can see from Scheme 1, the additives of water to the classic organic solvents were previously used in the reaction protocols for ways **B** and **C**.

On the other hand, the synthesis of benzimidazole derivatives fused with different heterocycles is a topic of numerous modern publications due to many biologically active compounds found within this class of heterocycles [16–19]. Thus, we were intrigued by a possibility to apply 2-(1*H*-benzo[*d*]imidaz-2-yl)acetonitrile (**9**) as an active methylene nitrile building block in reaction with enamines **2** within the general approach represented in Scheme 1.

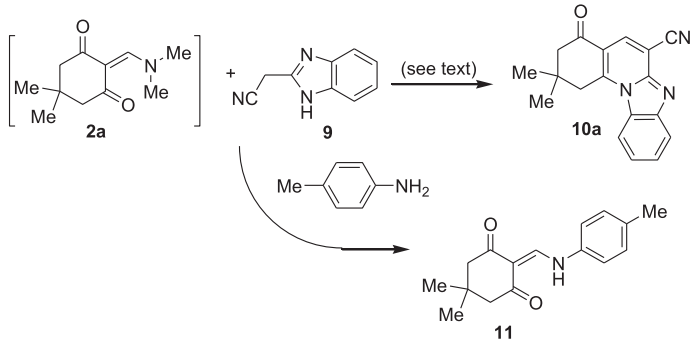
RESULTS AND DISCUSSION

Synthesis of a model enamine **2a** was carried out as described previously by stirring of a neat equimolar mixture of dimedone (**1a**) and DMFDMA during 5 min at room temperature (Scheme 2). The obtained product was used in further transformations without isolation. The reaction of this enamine with 2-benzoimidazylacetonitrile (**9**) under conditions of way **A** (Scheme 1) led to formation of the condensation product **10a** as described previously [9]. A wide variation of reaction conditions, including the reaction at 0°C or evaluated temperature (conventional or microwave heating, including conditions applied in way **B**) in the presence or absence of piperidine and in different solvents always led to the formation of **10a** as the main

Scheme 1. Reaction conditions for way **A**: *i*-PrOH, piperidine (cat.), microwave irradiation (MW) 100°C, 5 min [9]; way **B**: *i*-PrOH, piperidine (2.0 equiv), H_2O, MW 120°C, 10 min [10]; way **C**: MeCN, piperidine (2.0 equiv), HCl (aqueous, 18%, 8.0 equiv), rt, 30 min [11]; way **D**: isolated enolate **4**, $ArNH_2$ (1.1 equiv), AcOH, rt [13]. DMFDMA-dimethylformamide dimethylacetal.



Scheme 2. Reaction of enamine **2a** with 2-benzoimidazylacetonitrile (**9**).



product, and we were not able to isolate or even detect any products of other reaction pathways that could be expected based on the previously obtained results as illustrated in Scheme 1.

In an attempt to trap the intermediate enolate, we used *p*-toluidine in reactions with **2a** and **9** (by analogy with way **D** in Scheme 1); only enamine **11** or its mixture with **10a** were isolated after the reaction in acetic acid or in ethanol, respectively. Application of strong acidic conditions (by analogy with way **C** in Scheme 1) led to formation of unidentified reaction products. This data indicate the high selectivity of the studied transformation and higher reactivity of NH-nucleophile in benzimidazol fragment in the cyclization comparing with amide fragment in enolates **4** and thus leading to the formation of only one product **10a** under different reaction conditions.

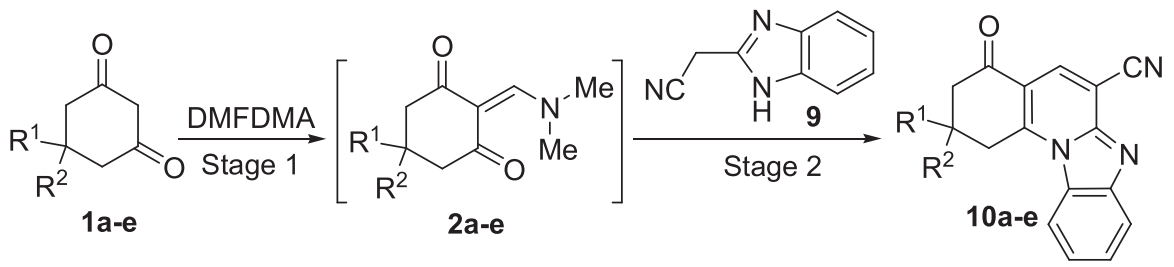
In the course of further screening reaction conditions for the consecutive one-pot interaction of dimedone (**1a**), DMFDMA, and 2-cyanomethylbenzimidazole (**9**), application of water as solvent without catalyst at room temperature during 1 h was found to give the highest yield (86%) of pure product **10a** easily separated from the reaction mixture by filtration. Application of microwave heating at 120°C during 5 min for this process gave a comparable product yield of 83%. It should be noted that this product was obtained earlier in isopropanol in the presence of piperidine under microwave irradiation at 100°C during 5 min with a yield of 78% (the conditions from way **A**, Scheme 1). Thus, further, we aimed to apply the found aqueous conditions for the synthesis of different benzo[4,5]imidazo[1,2-*a*]pyridine derivatives **10** from available 1,3-cyclohexandiones (**1b–e**).

The reaction with 1,3-cyclohexandione (**1b**) at room temperature or thermal heating in water or in isopropanol without catalyst led to a mixture of cyanide **10b** and initial 2-cyanomethylbenzimidazole (**9**). Pure product **10b** in good yield was obtained under microwave irradiation at 120°C during 5 min in water without catalyst. These conditions were also successfully used to obtain derivatives **10c** and **10d** (Table 1). In the case of initial diketone **1e**, an additional optimization step was required. In the first stage, the reaction of **1e** with DMFDMA required 1 h at room temperature for the completion, and for the second stage, isopropanol has to be used because of the law solubility of the intermediate enamine in water.

According to ^{1}H NMR spectra of the isolated products, all the obtained compounds did not require additional purification. Purity of compounds **10b** and **10c** over 99%

Table 1

Synthesis of compounds **10a–e**.



Product	R^1	R^2	Stage 1	Stage 2	Yield
10a	Me	Me	rt, 5 min	H_2O, rt, 1 h	86 (83[a])
10b	H	H	rt, 5 min	H_2O, MW, 120°C, 5 min	67
10c	H	2-Furyl	rt, 5 min	H_2O, MW, 120°C, 5 min	74
10d	H	3,4-di-OMe-C_6H_3	rt, 5 min	H_2O, MW, 120°C, 5 min	64
10e	H	4-OMe-C_6H_4	rt, 1 h	*i*-PrOH, MW, 120°C, 5 min	50

[a]The yield was obtained using H_2O, MW, 120°C, 5 min in Stage 2.

was additionally determined by LC-MS. The characterization data obtained by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, mass-spectrometry, and elemental analysis can be found in the Supporting Information.

CONCLUSION

Application of 2-cyanobenzimidazole in consecutive one-pot interaction with cyclic 1,3-diketones and DMFDMA under various conditions proceeds selectively leading to formation of 4-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]quinolin-6-yl cyanides (**10**). Water was found to be the optimal medium for the majority of the cases allowing facial synthesis and isolation of the pure products.

EXPERIMENTAL

General information. All solvents were used as acquired. Melting points were measured in open capillary tubes and are uncorrected. NMR spectra were recorded on a Bruker Avance drx 500 MHz (126 MHz for ^{13}C NMR; Bruker Spectrospin Ltd., Coventry, United Kingdom), Varian MR 400 MHz spectrometer (100 MHz for ^{13}C NMR), and Varian Mercury VX 200 MHz (Varian Inc., Palo Alto, CA) using DMSO-d_6 as solvent and residual solvent signal as the reference (TMS scale). Copies of NMR spectra were prepared with the help of ACD/NMR Processor (academic edition) program and are presented in the Supporting Information. IR spectra were recorded on a Perkin Elmer Spectrum One FTIR spectrometer (PerkinElmer, Inc., Shelton, CT) (pellets with potassium bromide KBr). The mass spectra were recorded on a Varian 1200 L GC-MS instrument with the use of direct exposure probe method with EI at 70 eV. LC-MS analyses were carried out with the use of chromatographic/mass-spectrometric system, which consist of HPLC chromatograph equipped with diode matrix and mass-selective detector, in the atmospheric pressure chemical ionization (negative or positive APCI) mode, simultaneous scanning of positive ions in mass 80–1,000 *m/z*. Elemental analysis was performed on a EuroVector EA-3000 instrument. All microwave experiments were carried out using the EmrysTM Creator EXP from Biotage (Uppsala, Sweden). All experiments were performed in sealed microwave process vials (for maximum 2.5 mL of the reaction mixture) utilizing the "High" absorbance level (150 W maximum power). Reaction times under microwave conditions reflect the time the reaction mixture was kept at the designated temperature (fixed hold time).

2-Cyanomethylbenzimidazole (**9**), dimedone (**1a**), and 1,3-cyclohexadione (**1b**) are commercially available compounds. Other substituted 1,3-cyclohexadiones **1c–e** were obtained using the known method [11]. The product **10a** was previously described [9].

General procedure for the synthesis of 4-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]quinoline-6-yl cyanides (10a–d). Enamines **2a–d** were obtained by a reaction of neat 1,3-cyclohexanediones (**1a–d**) (1.43 mmol) with DMFDMA (170 mg, 1.43 mmol) stirred at room temperature during 5 min in microwave process vial. To the obtained mixture, 2-cyanomethylbenzimidazole (**9**, 225 mg, 1.43 mmol) and 1.0 mL of water were added. The vial was encapsulated, and the reaction mixture

was heated under microwave irradiation at 120°C during 5 min in «High» mode (starting power is 150 W). After cooling, the precipitate obtained was filtered off and washed with water and small amount of isopropanol, then dried on air.

Procedure for the synthesis of 2,2-dimethyl-4-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]quinoline-6-yl cyanide (10a) at room temperature. Enamine **2a** was obtained by a reaction of neat dimedone (**1a**) (200 mg, 1.43 mmol) with DMFDMA (170 mg, 1.43 mmol) stirred at room temperature during 5 min. To the obtained mixture, 2-cyanomethylbenzimidazole (**9**, 225 mg, 1.43 mmol) and 1.0 mL of water were added. The obtained reaction mixture was stirred at room temperature during 1 h. The precipitate obtained was filtered off and washed with water and small amount of isopropanol, then dried on air. Yield: 355 mg (86%).

2,2-Dimethyl-4-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]quinoline-6-yl cyanide (10a). This compound was obtained as light-yellow crystals with the yield 86%, mp: 310–315°C (mp 330–333°C [9]); ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.48 (s, 1H), 8.44 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 3.71 (s, 2H), 2.61 (s, 2H), 1.18 (s, 6H).

4-Oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]quinoline-6-yl cyanide (10b). This compound was obtained as light-yellow crystals with the yield 67%, mp: 241–242°C (decomp.); IR (potassium bromide): 756, 1513, 1561, 1591, 1622, 1684, 2235, 3059 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.31–8.42 (m, 1H), 7.90–8.01 (m, 1H), 7.58–7.70 (m, 1H), 7.42–7.55 (m, 1H), 3.69–3.83 (m, 1H), 2.61–2.74 (m, 2H), 2.19–2.37 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 193.6, 155.8, 146.0, 145.0, 134.3, 130.1, 126.9, 123.0, 119.9, 116.8, 116.7, 115.2, 98.3, 35.8, 27.8, 20.2; LC-MS, purity >99%, *m/z* (APCI, pos.): 262.2 (M+H$^+$), *Anal.* Calcd ($C_{16}H_{11}N_3O$): C, 73.55; H, 4.24; N, 16.08. Found: C, 73.1; H, 4.2; N, 15.7.

2-Furyl-4-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]quinoline-6-yl cyanide (10c). This compound was obtained as light-yellow crystals with the yield 74%, mp: 286–288°C; IR (potassium bromide): 1512, 1563, 1592, 1624, 1682, 2236, 3068 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.53 (s, 1H), 8.42–8.56 (m, 1H), 8.34–8.40 (m, 1H), 7.94–8.01 (m, 1H), 7.61–7.70 (m, 2H), 7.49–7.57 (m, 1H), 6.37–6.46 (m, 2H), 4.16–4.26 (m, 1H), 3.88–4.02 (m, 2H), 2.94–3.08 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ: 192.2, 186.3, 155.1, 153.9, 146.1, 145.0, 142.4, 134.1, 130.1, 127.1, 123.3, 120.1, 116.8, 116.5, 115.1, 110.6, 105.9, 98.8, 32.1, 31.6; LC-MS: purity >99%, *m/z* (APCI, pos.) 328.2 (M+H$^+$); *Anal.* Calcd. ($C_{20}H_{13}N_3O_2$): C, 73.38; H, 4.00; N, 12.84. Found: C, 72.6; H, 4.1; N, 12.6.

2-(3′,4′-Dimethoxyphenyl)-4-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]quinoline-6-yl cyanide (10d). This compound was obtained as yellow crystals with the yield 64%, mp: 274–275°C; IR (potassium bromide): 1513, 1563, 1591, 1625, 1678, 2230, 3070 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.52 (s, 1H), 8.17–8.33 (m, 1H), 7.90–8.06 (m, 1H), 7.60–7.72 (m, 1H), 7.43–7.55 (m, 1H), 7.14 (br. s., 1H), 6.89–7.05 (m, 2H), 4.00–4.12 (m, 1H), 3.89–3.99 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.58–3.71 (m, 1H), 3.15 (s, 1H), 2.72–2.88 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ: 193.2, 154.9, 149.0, 148.1, 146.2, 145.0, 135.0, 134.2, 130.1, 127.1, 123.3, 120.1, 119.0, 116.9, 116.5, 115.2, 112.1, 111.4, 98.7, 55.65, 55.68, 43.0, 37.8, 35.3; MS: (70 eV, electron impact) *m/z* 397 (M$^+$); *Anal.* Calcd ($C_{24}H_{19}N_3O_3$): C, 72.53; H, 4.82; N, 10.57. Found: C, 73.4; H, 5.0; N, 10.7.

Procedure for the synthesis of 2-(4′-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]quinoline-6-yl cyanide (10e). Enamine **2e** was obtained by a reaction of neat 5-(4′-methoxyphenyl)-1,3-cyclohexanedione (**1e**, 312 mg, 1.43 mmol) with DMFDMA (170 mg, 1.43 mmol) stirred at room temperature during 1 h. To obtained the solution, 2-cyanomethylbenzimidazole (**9**) and 1.0 mL of isopropanol were added. The vial was encapsulated, and obtained reaction mixture was heated under microwave irradiation at 120°C during 5 min in «High» mode (starting power is 150 W). After cooling, the precipitate obtained was filtered off and washed with water and small amount of isopropanol, then dried on air. Yield: 169 mg (50%).

2-(4′-Methoxyphenyl)-4-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]quinoline-6-yl cyanide (10e). This compound was obtained as light-yellow crystals, mp: 244°C; IR (potassium bromide): 1511, 1559, 1588, 1621, 1684, 2235, 3056 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.41–8.63 (m, 1H), 8.12–8.35 (m, 1H), 7.83–8.10 (m, 1H), 7.56–7.71 (m, 1H), 7.33–7.54 (m, 3H), 6.84–7.09 (m, 2H), 3.80–4.16 (m, 2H), 3.75 (s, 3H), 3.51–3.71 (m, 1H), 2.97–3.19 (m, 1H), 2.64–2.86 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 35.6, 37.6, 43.4, 55.5, 99.0, 114.5, 115.5, 116.9, 117.2, 120.4, 123.6, 127.4, 128.6, 130.5, 134.6, 134.8, 145.3, 146.5, 155.3, 158.8, 193.5; MS (EI, 70 eV), *m/z*: 367 (M$^+$); *Anal.* Calcd ($C_{23}H_{17}N_3O_2$): C, 75.19; H, 4.66; N, 11.44. Found: C, 75.2; H, 4.8; N, 11.4.

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REFERENCES AND NOTES

[1] Green Techniques for Organic Synthesis and Medicinal Chemistry; Zhang, W.; Cue, B. Eds.; John Wiley & Sons: Weinheim, Germany, 2012; 768 p.

[2] Chanda, A.; Fokin, V. V. Chem Rev 2009, 109, 725.

[3] Butler, R. N.; Coyne, A. G. Chem Rev 2010, 110, 6302.
[4] Dallinger, D.; Kappe, C. O. Chem Rev 2007, 107, 2563.
[5] Dicks, A. P. Green Chem Lett Rev 2009, 2, 9.
[6] Kumaravel, K.; Vasuki, G. Curr Org Chem 2009, 13, 1820.
[7] Raj, M.; Singh, V. K. Chem Commun 2009 6687.
[8] Simon, M.-O.; Li, C.-J. Chem Soc Rev 2012, 41, 1415.
[9] Gorobets, N. Y.; Yousefi, B. H.; Belaj, F.; Kappe, C. O. Tetrahedron 2004, 60, 8633.
[10] Yermolayev, S. A.; Gorobets, N. Y.; Desenko, S. M. J Comb Chem 2009, 11, 44.
[11] Vodolazhenko, M. A.; Gorobets, N. Y.; Yermolayev, S. A.; Musatov, V. V.; Chebanov, V. A.; Desenko, S. M. RSC Adv 2012, 2, 1106.
[12] Dzhavakhishvili, S. G.; Gorobets, N. Y.; Chernenko, V. N.; Musatov, V. I.; Desenko, S. M. Russ Chem Bull 2008, 57, 422.
[13] Yermolayev, S. A.; Gorobets, N. Y.; Lukinova, E. V.; Shishkin, O. V.; Shishkina, S. V.; Desenko, S. M. Tetrahedron 2008, 64, 4649.
[14] Yermolayev, S. A.; Gorobets, N. Y.; Shishkin, O. V.; Shishkina, S. V.; Leadbeater, N. E. Tetrahedron 2011, 67, 2934.
[15] Gorobets, N. Y.; Sedash, Y. V.; Shishkina, S. V.; Shishkin, O. V.; Yermolayev, S. A.; Desenko, S. M. ARKIVOC 2009 23.
[16] Dawood, K. M.; Abdel-Wahabb, B. F. ARKIVOC 2010, 1, 333.
[17] Dawood, K. M.; Elwan, N. M.; Farahat, A. A.; Abdel-Wahab, B. F. J Heterocyclic Chem 2010, 47, 243.
[18] Dawood, K. M.; Elwan, N. M.; Abdel-Wahab, B. F. ARKIVOC 2011, 111.
[19] Bansal, Y.; Silakari, O. Bioorg Med Chem 2012, 20, 6208.