Tetrahedron 68 (2012) 3868–3874

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Isocyanide-based four-component synthesis of 1,3-indandionylamidinium betaines

Roya Akbarzadeh, Tayebeh Amanpour, Hamid Reza Khavasi, Ayoob Bazgir *

Department of Chemistry, Shahid Beheshti University, General Campus, Tehran 1983963113, Iran

ARTICLE INFO

Article history:
Received 6 December 2011
Received in revised form 19 February 2012
Accepted 12 March 2012
Available online 17 March 2012

Keywords:
Indandione
Isocyanide
1,3-Betaine
Amidinium

ABSTRACT

An efficient approach for the synthesis of novel 1,3-indandionylamidinium betaines via four-component reaction of 1,3-indandione, aldehydes, amines, and isocyanides, without assistance of any catalyst and under mild reaction conditions has been reported. The structures of these compounds were confirmed by IR, mass spectroscopic, ^{1}H NMR, ^{13}C NMR, and single-crystal X-ray diffraction studies.

1. Introduction

Multi-component reactions (MCRs) are of increasing importance in organic synthesis, because the strategies of MCR offer significant advantages over conventional linear-type syntheses.[1–3] The atom-economy, convergent character, operational simplicity, structural diversity, and complexity of the resultant products are the major advantages associated with multi-component reactions. Isocyanide-based multi-component reactions (IMCRs) are particularly interesting as they are more versatile and diverse than other MCRs.[4,5] The great potential of isocyanides for the development of multi-component reactions lies on the diversity of available bond forming processes, functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed. Thus MCRs involving isocyanides have emerged as valuable tools for the preparation of structurally diverse chemical libraries.[6–8]

1,3-Indanedione has proved to be a versatile starting material for the synthesis of potentially important compounds. 1,3-Indanedione and its derivatives have been employed in the synthesis of drugs,[9] in forensic chemistry for fingerprint detection,[10] in dyes and pigments,[11] and in semi- and photosemiconductors.[12] Furthermore, 1,3-indandione derivatives were demonstrated to be valuable precursors for strong electron acceptors.[13,14] Similarly, the amidine group is present in many compounds acting on a wide range of biological targets. It is an important pharmacophore in serine protease inhibitors,[15,16] fibrinogen receptor antagonists,[15–17] nitric oxide synthase inhibitors,[18] and tyrosine kinase inhibitors.[19] Amidine derivatives also possess antimicrobial activity.[20] They are also versatile synthetic intermediates that have been used for the further synthesis of heterocyclic compounds and as ligands for metal complexation.[21,22]

Despite continuous research for the development of new isocyanide-based multi-component reactions for the synthesis of various potentially important compounds,[6–8] to the best of our knowledge, no one has yet reported the synthesis of amidinium betaines via a multi-component strategy. Recently, the pseudo three-component synthesis of alkyl or arylamidine-acid zwitterionic compounds by the reaction of isocyanides and carboxylic acids was described by Shaabani and co-workers.[23]

As part of our program aimed at developing new isocyanide-based multi-component reactions,[24–26] herein, we describe, for the first time, an efficient synthetic approach to 1,3-indandionylamidinium betaines by an isocyanide-based four-component reaction.

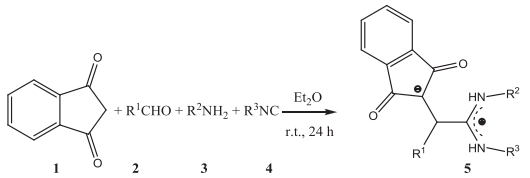
2. Results and discussion

The one-pot four-component condensation reactions of 1,3-indandione **1**, aldehydes **2**, amines **3**, and isocyanides **4** proceeded spontaneously at room temperature in Et_2O and were complete after 24 h to afford the corresponding 1,3-indandionylamidinium betaines **5** in good yields via the formation of three new bonds (two C–C and one C–N bonds) (Scheme 1). All the products were characterized by IR, mass, ^{1}H and ^{13}C NMR spectra, and elemental analysis.

The elucidation of the product structures are discussed here for **5a** as a representative example. The mass spectrum of **5a** shows the

* Corresponding author. Fax: +98 21 22431661; e-mail address: a_bazgir@sbu.ac.ir (A. Bazgir).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.03.039



Scheme 1. Synthesis of 1,3-indandionylamidinium betaines **5**.

expected molecular-ion peak at *m*/*z* 410. The IR spectrum of **5a** exhibits one broad absorption band due to carbonyl groups at 1623 cm^{-1}, and a broad absorption band for the NH groups is observed at 3191 cm^{-1}. The ^1H NMR spectrum of **5a** consists of a singlet signal for the *t*-Bu (δ_H 1.53 ppm) and one singlet for the methine group (δ_H 5.01 ppm). Two broad resonances (δ_H 9.87 and 12.53 ppm) are observed for the two NH groups. The aromatic hydrogen atoms give rise to characteristic signals in the aromatic region of the spectrum. The ^1H-decoupled ^{13}C NMR spectrum of **5a** showed 17 distinct signals, in agreement with the proposed structure.

To study the generality of the method, a library of fifteen substituted 1,3-indandionylamidinium betaines **5a**–**n** were selectively synthesized in good yields (Table 1). All compounds are stable solids whose structures were established by IR, Mass, ^1H, and ^{13}C NMR spectroscopy and elemental analysis. The structure of **5e** was confirmed by a single-crystal X-ray analysis[27] (Fig. 1).

To the best of our knowledge, this new isocyanide-based four-component strategy provides the first example of an efficient synthesis of indandionylamidinium betaines, is simple, and convenient, and would be applicable for the synthesis of different types of indandionylamidinium betaines. In addition, as the starting materials are readily accessible, a modular approach to the synthesis of indandionylamidinium betaines is possible. The work-up procedure of these reactions involves simply a filtration and crystallization from $CHCl_3$/hexane.

Mechanistically, the formation of amidinium betaines **5** can be rationalized by initial formation of 2-arylideneindenedione **6** through a Knoevenagel condensation reaction of **1** and **2**. Then, the intermediate **7** is produced by Michael-type addition reaction of **4** to **6**, followed by nucleophilic attack of **3** on the nitrilium moiety to produce intermediate **8**. Finally, H-shift produces the amidinium betaines **5** (Scheme 2).

Ferrocene derivatives have attracted special attention in recent years.[28] Due to the importance of ferrocenyl compounds, we used ferrocenecarboxaldehyde **9** within the developed process. This made it possible to synthesize new ferrocenyl amidinium betaines **10** (Scheme 3).

3. Conclusion

In conclusion, we have described for the first time a new and successful strategy for the convenient synthesis of 1,3-indandionylamidinium betaines via an isocyanide-based four-component reaction. The method offers several advantages including operational simplicity, good yields, and easy work-up procedures. Moreover, the reaction is performed under neutral conditions by simple mixing of the starting materials. It is worth noting that two C–C and one C–N bonds were formed with concomitant creation of amidinium betaines in this one-pot, four-component process.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. ^1H and ^{13}C NMR spectra were obtained on solutions in DMSO-d_6. IR spectra were recorded using a BOMEM MB-Series. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-*O*-Rapid analyzer. The chemicals used in this work were obtained from Fluka and Merck and were used without purification.

4.2. General procedure for the synthesis of 5

A mixture of 1,3-indandione (1 mmol), aldehyde (1 mmol), amine (1 mmol), and isocyanide (1 mmol) in Et_2O (5 mL) was stirred at room temperature for 24 h. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and the precipitate recrystallized from $CHCl_3$/hexane (1:3) to afford the pure product **5**.

*4.2.1. 2-(2-(tert-Butylamino)-1-phenyl-2-(phenylimino)ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5a**).* Yield (0.32 g, 78%) as a yellow solid, mp 194–196 °C; [found: C, 78.91; H, 6.31; N, 6.74. $C_{27}H_{26}N_2O_2$ requires C, 79.00; H, 6.38; N, 6.82]; ν_{max}(KBr) 3191, 1623, 1590 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.53 (9H, s, *t*-Bu), 5.01 (1H, s, CH), 7.04–7.48 (14H, m, Ar–H), 9.87 (1H, br s, N–H), 12.53 (1H, br s, N–H); δ_C (75 MHz, DMSO-d_6) 27.9, 41.8, 53.6, 101.1, 118.0, 126.8, 127.1, 128.4, 129.0, 129.2, 130.3, 136.2, 139.5, 140.7, 143.2, 166.3, 189.1; MS, *m*/*z*: 410 (M^+).

*4.2.2. 2-(2-(Cyclohexylimino)-1-phenyl-2-(phenylamino)ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5b**).* Yield (0.32 g, 74%) as a yellow solid, mp 252–254 °C; [found: C, 79.68; H, 6.38; N, 6.51. $C_{29}H_{28}N_2O_2$ requires C, 79.79; H, 6.46; N, 6.42]; ν_{max}(KBr) 3224, 1657, 1618 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.35–2.02 (10H, m, $5CH_2$ of cyclohexyl), 3.84 (1H, br s, CH–N), 5.09 (1H, s, CH), 7.12–7.49 (14H, m, Ar–H), 10.64 (1H, br s, N–H), 12.60 (1H, br s, N–H); δ_C (75 MHz, DMSO-d_6) 24.1, 25.1, 31.4, 31.6, 51.0, 101.3, 118.0, 127.0, 127.1, 127.6, 128.8, 128.9, 129.9, 130.3, 136.4, 139.6, 140.9, 166.3, 189.2; MS, *m*/*z*: 436 (M^+).

*4.2.3. 2-(2-(Cyclohexylamino)-1-(4-nitrophenyl)-2-(phenylimino) ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5c**).* Yield (0.34 g, 71%) as a yellow solid, mp 180–182 °C; [found: C, 72.21; H, 5.71; N, 8.80. $C_{29}H_{27}N_3O_4$ requires C, 72.33; H, 5.65; N, 8.73]; ν_{max}(KBr) 3231, 1640, 1591 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.34–1.57 (10H, m, $5CH_2$ of cyclohexyl), 3.87 (1H, br s, CH–N), 5.10 (1H, s, CH), 6.96–7.47 (13H, m, Ar–H), 10.83 (1H, br s, N–H), 12.50 (1H, br s, N–H); δ_C (75 MHz, DMSO-d_6) 24.1, 25.0, 31.1, 31.5, 51.6, 111.9, 123.8, 127.7, 128.1, 128.6, 129.1, 129.7, 130.1, 130.5, 132.5, 139.5, 149.8, 172.7, 189.1; MS, *m*/*z*: 481 (M^+).

*4.2.4. 2-(2-(2,6-Dimethylphenylamino)-1-phenyl-2-(phenylimino) ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5d**).* Yield (0.31 g, 68%) as a yellow solid, mp 165–167 °C; [found: C, 81.06; H, 5.65; N, 6.01. $C_{31}H_{26}N_2O_2$ requires C, 81.20; H, 5.72; N, 6.11]; ν_{max}(KBr) 3199, 1721, 1645 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 0.85 (6H, s, $2CH_3$), 3.88 (1H, s, CH), 6.71–7.58 (17H, m, Ar–H), 10.03 (1H, br s, N–H), 12.43 (1H, br s, N–H); MS, *m*/*z*: 458 (M^+). (Due to very low solubility of the product **5d**, we cannot report the ^{13}C NMR data for this product).

*4.2.5. 2-(1-(4-Bromophenyl)-2-(cyclohexylamino)-2-(phenylimino) ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5e**).* Yield (0.37 g, 73%) as a yellow solid, mp 178–180 °C; [found: C, 67.65; H, 5.33; N, 5.30. $C_{29}H_{27}BrN_2O_2$ requires C, 67.58; H, 5.28; N, 5.43]; ν_{max}(KBr) 3236, 1721, 1645 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.08–1.72 (10H, m, $5CH_2$ of cyclohexyl), 3.84 (1H, br s, CH–N), 5.03 (1H, s, CH), 7.06–7.47 (13H, m, Ar–H), 10.70 (1H, br s, N–H), 12.53 (1H, br s, N–H); δ_C (75 MHz, DMSO-d_6) 24.1, 25.1, 31.3, 31.6, 50.9, 101.0, 118.4,

Table 1
Synthesis of tetrazoles **5**

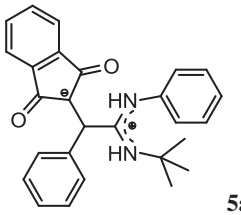
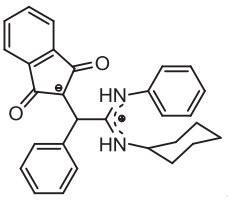
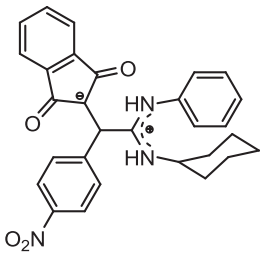
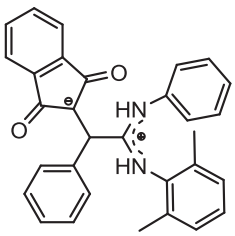
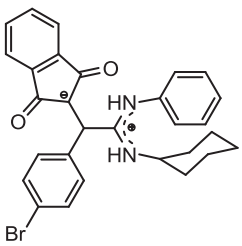
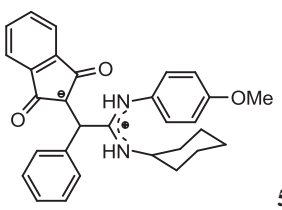
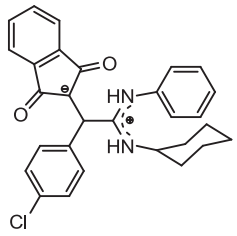
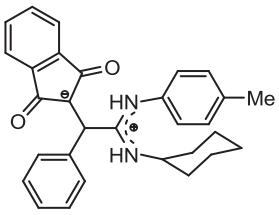
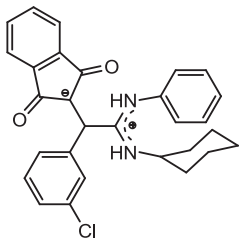
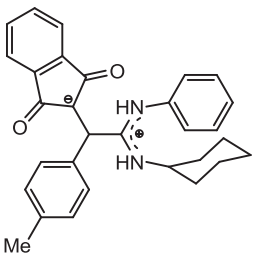
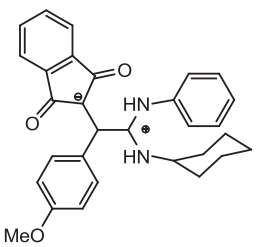
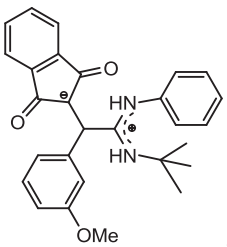
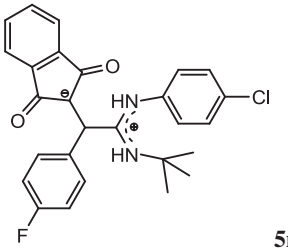
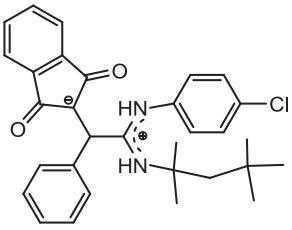
R^1	R^2	R^3	Product	Yield (%)
C_6H_5	C_6H_5	*tert*-Butyl	 **5a**	78
C_6H_5	C_6H_5	Cyclohexyl	 **5b**	74
4-NO_2–C_6H_4	C_6H_5	Cyclohexyl	 **5c**	71
C_6H_5	C_6H_5	2,6-Dimethylphenyl	 **5d**	68
4-Br–C_6H_4	C_6H_5	Cyclohexyl	 **5e**	73
C_6H_5	4-MeO–C_6H_4	Cyclohexyl	 **5f**	69

Table 1 (*continued*)

R^1	R^2	R^3	Product	Yield (%)
4-Cl–C_6H_4	C_6H_5	Cyclohexyl	 **5g**	76
C_6H_5	4-Me–C_6H_4	Cyclohexyl	 **5h**	79
3-Cl–C_6H_4	C_6H_5	Cyclohexyl	 **5i**	69
4-Me–C_6H_4	C_6H_5	Cyclohexyl	 **5j**	78
4-MeO–C_6H_4	C_6H_5	Cyclohexyl	 **5k**	69
3-MeO–C_6H_4	C_6H_5	*tert*-Butyl	 **5l**	73

(*continued on next page*)

Table 1 (*continued*)

R^1	R^2	R^3	Product	Yield (%)
4-F–C_6H_4	4-Cl–C_6H_4	*tert*-Butyl	 **5m**	64
C_6H_5	4-Cl–C_6H_4	1,1,3,3-Tetramethyl-buty	 **5n**	68

120.3, 123.6, 127.7, 128.9, 129.2, 130.0, 131.8, 136.3, 139.4, 140.3, 165.8, 189.1; MS, *m*/*z*: 516 (M^+), 514 (M^+).

4.2.6. 2-(2-(Cyclohexylamino)-2-(4-methoxyphenylimino)-1-phenylethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (***5f***). Yield (0.32 g, 69%) as a yellow solid, mp 163–165 °C; [found: C, 77.33; H, 6.56; N, 5.93. $C_{30}H_{30}N_2O_3$ requires C, 77.23; H, 6.48; N, 6.00]; ν_{max}(KBr) 3225, 1644, 1640 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.31–1.73 (10H, m, $5CH_2$ of cyclohexyl), 3.62 (1H, br s, CH–N), 3.79 (3H, s, MeO), 5.03 (1H, s, CH), 7.00–7.49 (13H, m, Ar–H), 10.47 (1H, br s, N–H), 12.48 (1H, br s, N–H). δ_C (75 MHz, DMSO-d_6) 24.1, 25.1, 31.3, 31.5, 50.8, 55.8, 101.4, 114.9, 118.0, 126.9, 127.1, 128.7, 128.9, 129.0, 130.3, 139.5, 140.9, 159.3, 166.6, 189.1; MS, *m*/*z*: 465 (M^+).

4.2.7. 2-(1-(4-Chlorophenyl)-2-(cyclohexylamino)-2-(phenylimino) ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (***5g***). Yield (0.35 g, 76%) as a yellow solid, mp 188–190 °C; [found: C, 73.86; H, 5.82; N, 5.95. $C_{29}H_{27}ClN_2O_2$ requires C, 73.95; H, 5.78; N, 5.95]; ν_{max}(KBr) 3448, 1644, 1590 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.22–1.78 (10H, m, $5CH_2$ of cyclohexyl), 3.61 (1H, br s, CH–N), 5.02 (1H, s, CH), 6.86–7.42 (13H, m, Ar–H), 10.43 (1H, br s, N–H), 11.87 (1H, br s, N–H); δ_C (75 MHz, DMSO-d_6) 24.2, 25.3, 31.5, 31.8, 50.5, 101.5, 117.5, 117.9, 126.8, 127.4, 128.9, 129.8, 130.0, 130.2, 131.5, 139.6, 140.4, 164.7, 189.2; MS, *m*/*z*: 470 (M^+).

4.2.8. 2-(2-(Cyclohexylamino)-1-phenyl-2-(p-tolylimino)ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (***5h***). Yield (0.35 g, 79%) as a yellow solid, mp 234–236 °C; [found: C, 79.88; H, 6.79; N, 6.12. $C_{30}H_{30}N_2O_2$ requires C, 79.97; H, 6.71; N, 6.22]; ν_{max}(KBr) 3231, 1654, 1606 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.26–1.67 (10H, m, $5CH_2$ of cyclohexyl), 1.83 (3H, s, Me), 3.62 (1H, br s, CH–N), 5.04 (1H, s, CH), 6.76–7.20 (13H, m, Ar–H), 10.28 (1H, br s, N–H), 11.83 (1H, br s,

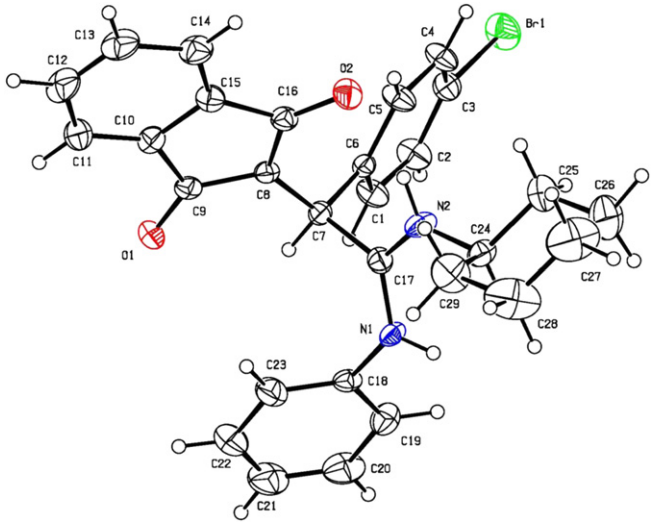
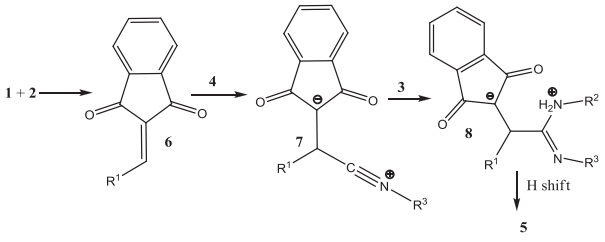
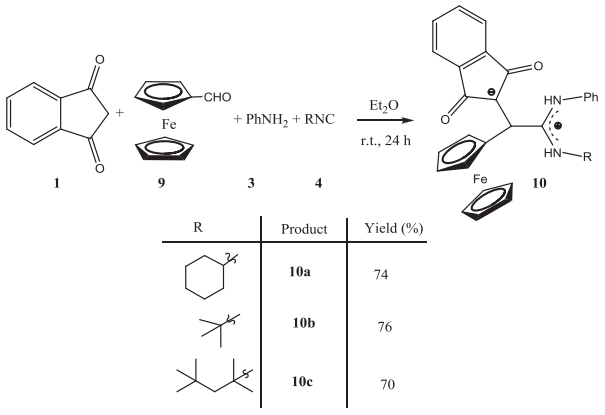


Fig. 1. X-ray crystal structure of **5e**.



Scheme 2. Proposed mechanism.



R	Product	Yield (%)
	10a	74
	10b	76
	10c	70

Scheme 3. Synthesis of ferrocenyl amidinium betaines **10**.

N–H); δ_C (75 MHz, DMSO-d_6) 20.9, 24.4, 25.5, 31.7, 31.9, 49.4, 102.9, 117.5, 118.0, 124.9, 126.1, 127.2, 128.3, 129.8, 131.7, 140.2, 142.8, 143.5, 164.1, 189.3; MS, *m*/*z*: 450 (M^+).

*4.2.9. 2-(1-(3-Chlorophenyl)-2-(cyclohexylamino)-2-(phenylimino) ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5i**).* Yield (0.32 g, 69%) as a yellow solid, mp 228–230 °C; [found: C, 73.83; H, 5.67; N, 6.04. $C_{29}H_{27}ClN_2O_2$ requires C, 73.95; H, 5.78; N, 5.95]; ν_{max}(KBr) 3222, 1641, 1584 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.27–1.67 (10H, m, $5CH_2$ of cyclohexyl), 3.67 (1H, br s, CH–N), 5.05 (1H, s, CH), 6.85–7.35 (13H, m, Ar–H), 10.23 (1H, br s, N–H), 11.07 (1H, br s, N–H); δ_C (75 MHz, DMSO-d_6) 24.3, 25.4, 31.6, 31.9, 50.0, 101.8, 117.9, 125.8, 125.9, 126.6, 126.9, 129.5, 129.7, 130.1, 130.5, 133.2, 139.7, 142.0, 144.5, 163.1, 189.3; MS, *m*/*z*: 471 (M^+).

*4.2.10. 2-(2-(Cyclohexylamino)-2-(phenylimino)-1-p-tolylethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5j**).* Yield (0.35 g, 78%) as an orange solid, mp 156–158 °C; [found: C, 79.91; H, 6.67; N, 6.15. $C_{30}H_{30}N_2O_2$ requires C, 79.97; H, 6.71; N, 6.22]; ν_{max}(KBr) 3212, 1643, 1623 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.23–1.68 (10H, m, $5CH_2$ of cyclohexyl), 1.87 (3H, s, CH_3), 3.67 (1H, br s, CH–N), 5.04 (1H, s, CH), 7.01–7.36 (13H, m, Ar–H), 10.03 (1H, br s, N–H), 10.90 (1H, br s, N–H); δ_C (75 MHz, DMSO-d_6) 20.9, 24.3, 25.5, 31.7, 32.0, 49.9, 102.7, 117.6, 125.8, 127.1, 129.1, 129.4, 129.9, 135.4, 139.1, 140.0, 142.6, 162.8, 164.1, 189.3; MS, *m*/*z*: 450 (M^+).

*4.2.11. 2-(2-(Cyclohexylamino)-1-(4-methoxyphenyl)-2-(phenylimino)ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5k**).* Yield (0.32 g, 69%) as a yellow solid, mp 174–176 °C; [found: C, 77.13; H, 6.55; N, 5.91. $C_{30}H_{30}N_2O_3$ requires C, 77.23; H, 6.48; N, 6.00]; ν_{max}(KBr) 3237, 1646, 1618 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.07–1.91 (10H, m, $5CH_2$ of cyclohexyl), 3.67 (1H, br s, CH–N), 3.79 (3H, s, MeO), 5.01 (1H, s, CH), 6.79–7.46 (13H, m, Ar–H), 10.55 (1H, br s, N–H), 12.59 (1H, br s, N–*H*); δ_C (75 MHz, DMSO-d_6) 24.1, 25.1, 31.6, 35.9, 51.4, 55.4, 101.6, 114.3, 117.9, 127.7, 128.1, 128.7, 129.9, 130.2, 132.9, 139.6, 158.4, 166.6, 167.0, 189.1; MS, *m*/*z*: 466 (M^+).

*4.2.12. 2-(2-(tert-Butylamino)-1-(3-methoxyphenyl)-2-(phenylimino)ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5l**).* Yield (0.32 g, 73%) as an orange solid, mp 196–198 °C; [found: C, 76.21; H, 6.34; N, 6.25. $C_{28}H_{28}N_2O_3$ requires C, 76.34; H, 6.41; N, 6.36]; ν_{max}(KBr) 3223, 1657, 1613 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.52 (9H, s, *t*-Bu), 3.64 (3H, s, MeO), 4.97 (1H, s, CH), 6.54–7.49 (13H, m, Ar–H), 9.86 (1H, br s, N–H), 12.56 (1H, br s, N–H). δ_C (75 MHz, DMSO-d_6) 27.9, 41.8, 53.6, 55.3, 101.1, 112.1, 112.8, 118.0, 119.1, 128.4, 129.2, 129.9, 130.1, 130.3, 136.2, 139.5, 142.2, 159.5, 166.1, 189.1; MS, *m*/*z*: 440 (M^+).

*4.2.13. 2-(2-(tert-Butylamino)-2-(4-chlorophenylimino)-1-(4-fluorophenyl)ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5m**).* Yield (0.29 g, 64%) as a cream solid, mp 218–220 °C; [found: C, 69.91; H, 5.13; N, 6.16. $C_{27}H_{24}ClFN_2O_2$ requires C, 70.05; H, 5.23; N, 6.05]; ν_{max}(KBr) 3251, 1683, 1654 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.23 (9H, s, *t*-Bu), 5.30 (1H, s, CH), 7.00–7.92 (12H, m, Ar–H), 10.12 (1H, br s, N–H), 12.66 (1H, br s, N–H); δ_C (75 MHz, DMSO-d_6) 32.3, 42.1, 53.8, 103.5, 120.6, 120.9, 125.0, 126.3, 129.3, 133.2, 134.6, 137.2, 139.0, 142.1, 145.6, 171.7, 197.3; MS, *m*/*z*: 462 (M^+).

*4.2.14. 2-(2-(4-Chlorophenylimino)-1-phenyl-2-(2,4,4-trimethylpentan-2-ylamino)ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**5n**).* Yield (0.34 g, 68%) as a cream solid, mp 204–206 °C; [found: C, 74.23; H, 6.59; N, 5.51. $C_{31}H_{33}ClN_2O_2$ requires C, 74.31; H, 6.64; N, 5.59]; ν_{max}(KBr) 3247, 1662, 1605. δ_H (300 MHz, DMSO-d_6) 0.69 (9H, s, 3CH_3), 1.01 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.37 (2H, ABq, *J* 6.3 Hz, CH_2), 5.28 (1H, s, CH), 7.13–8.29 (13H, m, Ar–H), 10.21 (1H, br s, N–H), 11.78 (1H, br s, N–H). δ_C (75 MHz, DMSO-d_6) 28.4, 29.0, 31.3, 31.5, 35.6, 42.2, 54.7, 101.3, 123.4, 124.2, 127.7, 127.9, 128.3, 128.8, 130.9, 133.1, 133.2, 139.6, 140.2, 168.8, 189.0; MS, *m*/*z*: 501 (M^+).

*4.2.15. 2-(2-(Cyclohexylamino)-1-ferrocenyl-2-(phenylimino)ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**10a**).* Yield (0.39 g, 74%) as a purple solid, mp 163–165 °C; [found: C, 72.69; H, 5.85; N, 5.25. $C_{33}H_{32}FeN_2O_2$ requires C, 72.80; H, 5.92; N, 5.15]; ν_{max}(KBr) 3495, 1656, 1624 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.26–1.81 (10H, m, $5CH_2$ of cyclohexyl), 3.77–4.24 (10H, m, CH_{fer} and CH–N), 5.02 (1H, s, CH), 7.17–7.88 (9H, m, Ar–H), 10.47 (1H, br s, N–H), 11.94 (1H, br s, N–H); MS, *m*/*z*: 544 (M^+). (Due to very low solubility of the product **10a**, we cannot report the ^{13}C NMR data for this product).

*4.2.16. 2-(2-(tert-Butylamino)-1-ferrocenyl-2-(phenylimino)ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**10b**).* Yield (0.39 g, 76%) as a yellow solid, mp 176–178 °C; [found: C, 71.73; H, 5.77; N, 5.35. $C_{31}H_{30}FeN_2O_2$ requires C, 71.82; H, 5.83; N, 5.40]; ν_{max}(KBr) 3254, 1650, 1616 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.64 (9H, s, *t*-Bu), 3.47–4.23 (9H, m, CH_{fer}), 5.16 (1H, s, CH), 7.13–7.85 (9H, m, Ar–H), 10.93 (1H, br s, N–H), 12.08 (1H, br s, N–H); MS, *m*/*z*: 518 (M^+). (Due to very low solubility of the product **10b**, we cannot report the ^{13}C NMR data for this product).

*4.2.17. 2-(1-Ferrocenyl-2-(phenylimino)-2-(2,4,4-trimethylpentan-2-ylamino)ethyl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**10c**).* Yield (0.4 g, 70%) as a yellow solid, mp 179–181 °C; [found: C, 73.03; H, 6.56; N, 4.80. $C_{35}H_{38}FeN_2O_2$ requires C, 73.17; H, 6.67; N, 4.88]; ν_{max}(KBr) 3242, 1623, 1588 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 0.82 (9H, s, $3CH_3$), 1.39 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.63 (2H, ABq, *J* 11.9 Hz, CH_2), 3.89–4.21 (9H, m, CH_{fer}), 5.01 (1H, s, CH), 7.17–7.68 (9H, m, Ar–H), 9.56 (1H, br s, N–H), 11.84 (1H, br s, N–H); δ_C (75 MHz, DMSO-d_6) 29.0, 31.2, 31.6, 36.4, 39.1, 49.6, 56.8, 67.1, 67.4, 67.7, 69.0, 89.6, 100.0, 117.9, 128.9, 129.0, 129.9, 130.1, 136.5, 166.9, 189.4; MS, *m*/*z*: 574 (M^+).

Acknowledgements

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

References and notes

1. *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.
2. Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634.
3. Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980.
4. Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.
5. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
6. Shaabani, A.; Maleki, A.; Rezayan, A. H.; Sarvary, A. *Mol. Divers.* **2011**, *15*, 41–68.
7. Sadjadi, S.; Heravim, M. M. *Tetrahedron* **2011**, *67*, 2707–2752.
8. Ivachtchenko, A. V.; Ivanenkov, Y. A.; Kysil, V. M.; Krasavin, M. Y.; Ilyin, A. P. *Russ. Chem. Rev. (Engl. Transl.)* **2010**, *79*, 787–817.
9. Leblois, D.; Piessard, S.; Le Baut, G.; Kumar, P.; Brion, J. D.; Sparfel, L.; Sanchez, R. Y.; Juge, M.; Petit, J. Y.; Welin, L. *Eur. J. Med. Chem.* **1987**, *22*, 229–288.
10. Hansen, D. B.; Joulie, M. M. *Chem. Soc. Rev.* **2005**, *34*, 408–417.
11. Bello, K.; Cheng, L.; Griffiths, J. *J. Chem. Soc., Perkin Trans. 2* **1987**, 815–818.
12. Bryce, M. R.; Davies, S. R.; Hasan, M.; Ashwell, G. J.; Szablewski, M.; Drew, M. G.; Short, R.; Hursthouse, M. B. *J. Chem. Soc, Perkin Trans. 2* **1989**, 1285–1292.
13. Khodorkovsky, V.; Ellern, A.; Neilands, O. *Tetrahedron Lett.* **1994**, *35*, 2955–2958.
14. Khodorkovsky, V.; Ellern, A.; Shapiro, L.; Neilands, O. *Tetrahedron Lett.* **1999**, *40*, 4851–4854.
15. Rewinkel, J. B. M.; Adang, A. E. P. *Curr. Pharm. Des.* **1999**, *5*, 1043–1075.
16. Scarborough, R. M.; Gretler, D. D. *J. Med. Chem.* **2000**, *43*, 3453–3473.
17. Sielecki, T. M.; Liu, J.; Mousa, S. A.; Racanelli, A. L.; Hausner, E. A.; Wexler, R. R.; Olson, R. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2201–2204.
18. Collins, J. L.; Shearer, B. G.; Oplinger, J. A.; Lee, S.; Garvey, E. P.; Salter, M.; Dufry, C.; Burnette, T. C.; Furtine, E. S. *J. Med. Chem.* **1998**, *41*, 2858–2871.
19. Nakamura, H.; Sasaki, Y.; Uno, M.; Yoshikawa, T.; Asano, T.; Ban, H. S.; Fukazawa, H.; Shibuya, M.; Uehara, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5127–5131.

20. Stephens, C. E.; Tanious, E.; Kim, S.; Wilson, D. W.; Schell, W. A.; Perfect, J. R.; Franzblau, S. G.; Boykin, D. W. *J. Med. Chem.* **2001**, *44*, 1741–1748.
21. Boyd, G. V. In; Patai, S., Rappoport, Z., Eds. *The Chemistry of Amidines and Imidates*; Wiley: New York, NY, 1991; Vol. 2; (Chapter 8).
22. Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038–2039.
23. Shaabani, A.; Rezayan, A. H.; Sarvary, A.; Keshipour, S.; Khavasi, H. R. *Tetrahedron Lett.* **2010**, *51*, 4091–4094.
24. Akbarzadeh, R.; Mirzaei, P.; Bazgir, A. *J. Organomet. Chem.* **2010**, *695*, 2320–2324.
25. Akbarzadeh, R.; Amanpour, T.; Mirzaei, P.; Bazgir, A. *J. Organomet. Chem.* **2011**, *696*, 3421–3424.
26. Akbarzadeh, R.; Amanpour, T.; Mirzaei, P.; Bazgir, A. *Helv. Chim. Acta* **2011**, *94*, 1527–1532.
27. X-ray data for **5e**: $C_{29}H_{27}Br_1N_2O_2$, M=515.43 g/mol, monoclinic system, space group $P2_1/c$, a=11.1140(5), b=18.7276(7), c=12.8834(6) Å, β=107.491(4)°, V=2557.55(19) Å^3, Z=4, D_{calcd}=1.339 g cm^{-3}, μ(MoKα)=1.635 mm^{-1}, crystal dimension of 0.30×0.07×0.05 mm. The structure was solved by using SHELXS. The structure refinement and data reduction was carried out with SHELXL of the X-Step32 suite of programs.[29] The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1=0.1182, wR_2=0.2226 and S=1.170 with 315 parameters using 6914 independent reflection (θ range=1.92–29.30°). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data for **5e** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 855656, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
28. Torres, J. C.; Pilli, R. A.; Vargas, M. D.; Violante, F. A.; Garden, S. J.; Pinto, A. C. *Tetrahedron* **2002**, *58*, 4487–4492 and references cited therein.
29. X-STEP32 Version 1.07b, X-ray Structure Evaluation Package; Stoe & Cie: Darmstadt, Germany, 2000.