C. R. Chimie 17 (2014) 156–163

Contents lists available at SciVerse ScienceDirect

Comptes Rendus Chimie

www.sciencedirect.com

Full paper/Mémoire

An expedient approach for the regio- and stereoselective synthesis of novel spiroindolizidines via [3+2] cycloaddition

Kamal Alimohammadi [a], Yaghoub Sarrafi [b,*], Bahareh Rajabpour [b]

[a] Department of Chemistry, Dr. Shariati Branch, University of Farhangian, Sari, Iran
[b] Department of Organic Chemistry, Faculty of Chemistry, University of Mazandaran, 47416 Babolsar, Iran

ARTICLE INFO

Article history:
Received 6 May 2013
Accepted after revision 21 June 2013
Available online 15 August 2013

Keywords:
1,3-Dipolar cycloaddition
Azomethine ylide
Indolizidines
Spiro compounds
1,5-Prototropic shift

ABSTRACT

A new series of spiroindolizidines was synthesized by one-pot, three-component condensation of azomethine ylides, generated from 1,2,3,4-tetrahydroisoquinoline with ninhydrin or isatin derivatives by a 1,5-prototropic shift route, with various derivatives of *trans*-β-nitrostyrene in a regio- and stereoselective manner. X-ray crystal structure analysis and NMR spectroscopic data confirmed the structure outcome of the cycloaddition reaction.

1. Introduction

Multicomponent reactions (MCRs) have developed as a powerful tool for delivering the molecular diversity needed in the combinatorial approaches for the synthesis of interesting heterocyclic scaffolds [1]. The MCRs are highly convergent processes that have been extensively employed in the synthesis of complex molecules that are particularly useful for the creation of diverse chemical libraries of 'drug-like' molecules for biological screening [2].

Indolizidines with different degrees of unsaturation constitute the core structural element found in a large family of natural alkaloids that occupy an important and privileged position in modern organic chemistry due to their remarkable and attractive pharmacological properties [3]. The indolizidine ring systems and spirooxindole derivatives containing the indolizidine moiety, found in a large number of compounds, display important biological activities, as exemplified by those shown in Fig. 1 [4,5].

In order to understand the structure–activity relationship (SAR) as well as to improve the efficacy of the indolizidine skeleton as an anticancer agent and biologically active molecules, a flexible approach for the synthesis of different derivatives of these classes of molecules is in great demand. Recently, many synthetic methods have been developed for the synthesis of new pyrrolidine and indolizidine alkaloids that were found to exhibit superior biological and pharmacological activities with therapeutic potential [6].

1,3-Dipolar cycloadditions are fundamental processes in organic chemistry, and have taken an important place as a synthetic strategy for the synthesis of bioactive compounds [7], natural products, and alkaloids [8]. 1,3-Dipolar cycloaddition of azomethine ylides with various dipolarophiles become extremely interesting when the absolute configuration of the newly created stereocentres can be controlled in an enantio- and stereoselective manner [9,10]. These aspects of azomethine ylides have been successfully applied in the total synthesis of biologically interesting molecules.

Nitropyrrolidines have been synthesized by various methods, starting from nitro olefins [11]. Recently, the synthesis of spiropyrrolidines from the reaction between

* Corresponding author. Tel./fax: +98 1125342350.
E-mail address: ysarrafi@umz.ac.ir (Y. Sarrafi).

1631-0748/$ – see front matter
http://dx.doi.org/10.1016/j.crci.2013.06.003

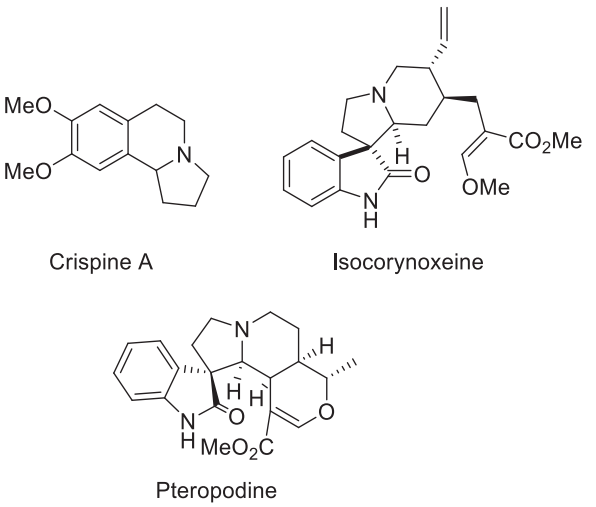


Fig. 1. Biologically important molecules containing the indolizidine ring.

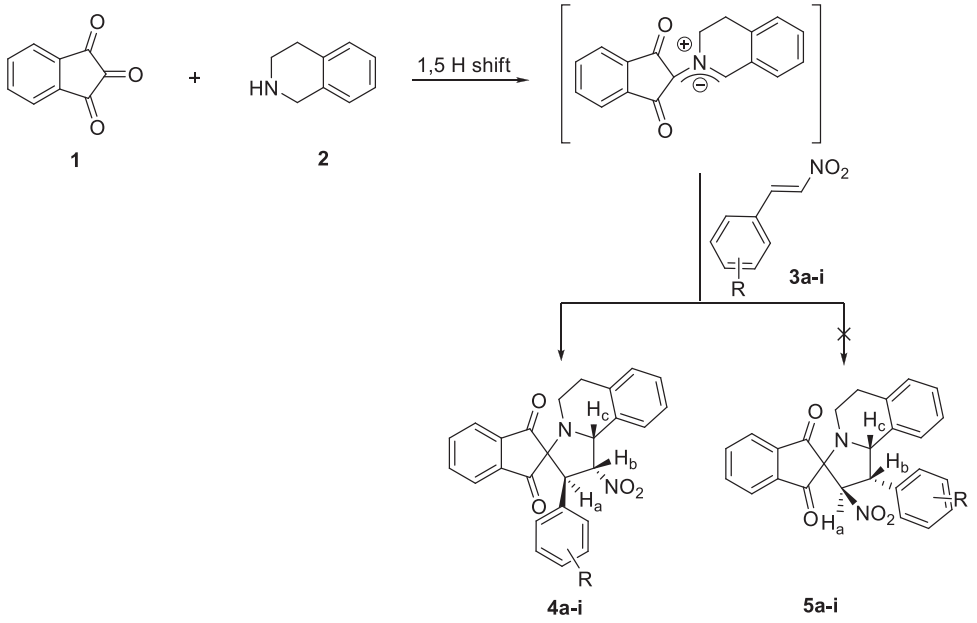
β-nitrostyrene and the azomethine ylides generated decarboxylatively from isatin/ninhydrin and sarcosine/proline was reported [12]. However, among several methods available for generating azomethine ylides [13], only a few reports on its preparation through 1,5-prototropic shift have so far appeared in the literature [14]. In this regard, and as a part of our program aimed at developing studies in the synthesis of heterocyclic systems by 1,3-dipolar cycloaddition reaction [14,15], we studied the regio- and stereoselective synthesis of novel spiroindolizidines via the one-pot, three-component condensation of *trans*-β-nitrostyrenes with azomethine ylides generated by a 1,5-prototropic shift route.

2. Results and discussion

In our first attempt, the reaction of ninhydrin **1** with 1,2,3,4-tetrahydroisoquinoline **2** in boiling ethanol led to the formation, by a 1,5-prototropic shift route, of an azomethin ylide that readily underwent a 1,3-dipolar cycloaddition reaction with β-nitrostyrene **3a** to give a single cycloadduct **4a** (Scheme 1). Encouraged by this success, we extended the scope to the reaction of ninhydrin **1** and 1,2,3,4-tetrahydroisoquinoline **2** with various derivatives of β-nitrostyrene **3b–i** with both electron-withdrawing and electron releasing-substituents under similar conditions; the corresponding novel spiroindolizidines **4b–i** containing the oxindole ring system were synthesized in high yields (Table 1).

The structures and regiochemistry of the cycloadducts were established by spectral analysis. The ^{1}H NMR spectrum of **4a** evidenced two doublets at δ 4.47 (J = 5.2 Hz) and δ 5.61 (J = 6.8 Hz) for H_a and H_c protons, respectively. The $CHNO_2$ proton H_b resonated at δ 6.56 (J = 5.2, 6.8 Hz), as a doublet of doublet (not a doublet, as expected for **5a**), which clearly confirmed the correct regiochemistry of the product **4a** (Scheme 1). The ^{13}C NMR showed a signal at δ 64.8 ppm due to the spiro carbon and two peaks at δ 198.3 and δ 201.1 ppm for the ninhydrin carbonyl carbons.

In contrast with our previous report [13], in which we subjected (*E*)-1-phenyl-2-nitropropene **6** to these reaction conditions, no regioselectivity inversion was observed and the corresponding spiroindolizidine **7** was obtained as a sole product in 84% yield (Scheme 2). In the ^{1}HNMR spectrum of **7**, the appearance of two singlets attributed to the H_a and H_b protons instead of two doublets expected for regioisomer **8** clearly confirms the correct regiochemistry of the cycloaddition reaction.



Scheme 1. Regioselective synthesis of spiroindolizidines **4a–i**.

Table 1
Synthesis of spiroindolizidines **4a–i**.

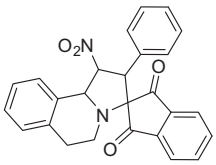
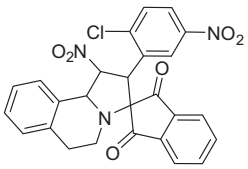
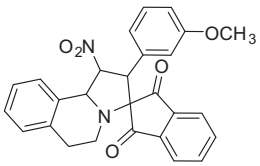
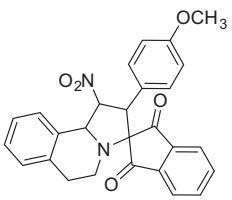
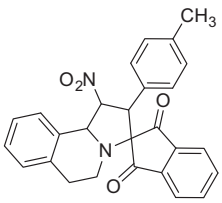
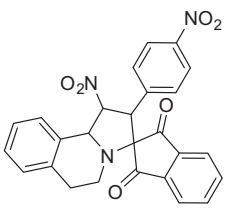
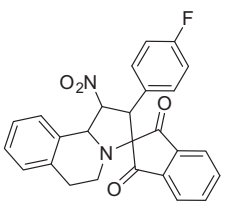
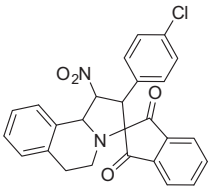
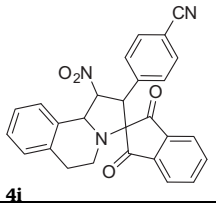
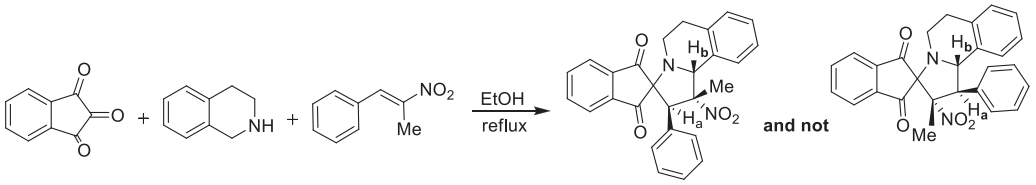
Entry	R^1	Product	Yield[a] (%)
1	H	 **4a**	92
2	2-Cl, 5-NO_2	 **4b**	94
3	*m*-OCH_3	 **4c**	92
4	*p*-OCH_3	 **4d**	88
5	*p*-CH_3	 **4e**	82
6	*p*-NO_2	 **4f**	84
7	*p*-F	 **4g**	87

Table 1 (*Continued*)

Entry	R^1	Product	Yield[a] (%)
8	*p*-Cl	 **4h**	95
9	*p*-CN	 **4i**	92

[a] Isolated yield.



Scheme 2. Regioselective synthesis of spiroindolizidine **7**.

The structure and regiochemistry of the spirocycloadduct **4d** was further confirmed through X-ray diffraction studies (Fig. 2). The ORTEP diagram of **4d** indicates that the cycloaddition proceeded via an endo-transition state. The proposed mechanism is shown in Scheme 3.

Furthermore, the possibility of the formation of other stereoisomer via an *exo*-transition state was ruled out with a differential NOE experiment carried out on **7**. The irradiation of CH_3 enhances the signal of H_b, while no correlation was observed between CH_3 and H_a. This observation reveals the *cis* disposition of the methyl group with H_b and a *trans* geometry with H_a. Therefore, the correct stereochemistry of compound **7** is shown in Fig. 3.

In addition, to explore the potential of this protocol in spiroheterocycle synthesis, the reaction of 1,2,3,4-tetrahydroisoquinoline **2** and isatin derivatives **9a–d** with β-nitrostyrene **3a** and β-methyl-β-nitrostyrene **6** was investigated in a one-pot three-component process (Scheme 4). The reaction afforded a series of novel spiroindolizidines **10a–h** as major products in a similar regio- and stereocontrolled manner (Table 2).

The structure of the isolated products, fully characterized by the spectroscopic data, was found consistent with the assigned structure. The stereochemistry of cycloadduct **10h** was unequivocally determined by single-crystal X-ray

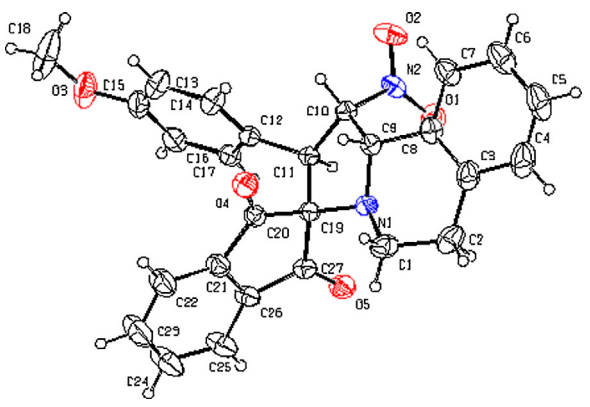


Fig. 2. ORTEP diagram of **4d**. Color available online.

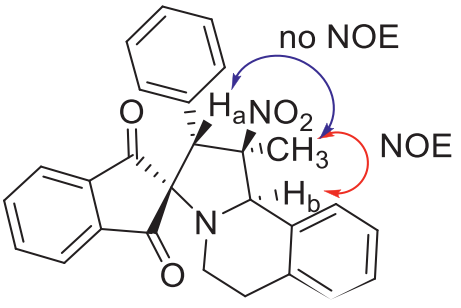
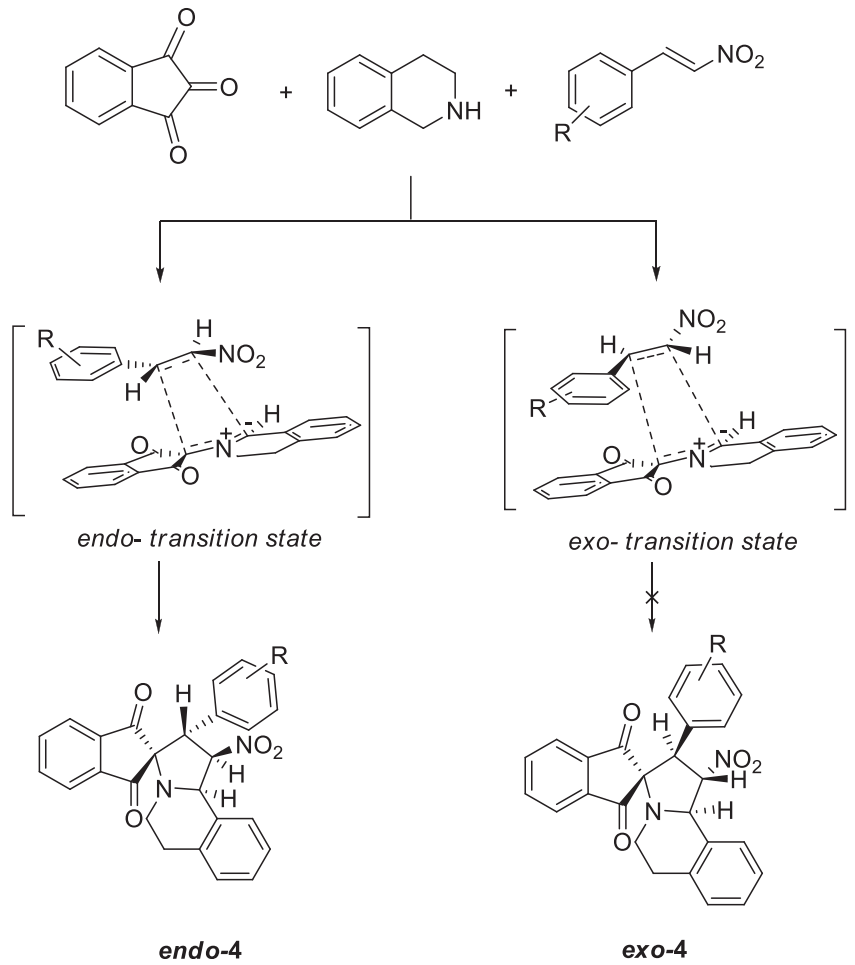


Fig. 3. NOE correlations of cycloadduct **7**.



Scheme 3. Proposed mechanism for the synthesis of spiroindolizidines.

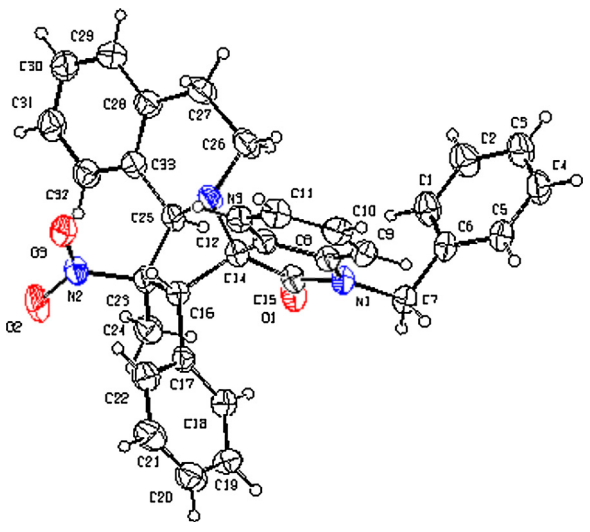


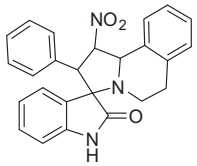
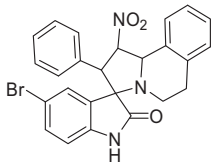
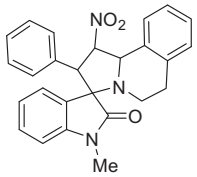
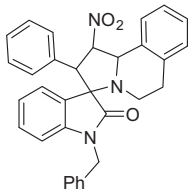
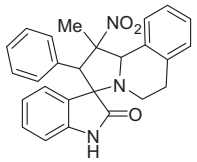
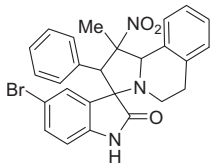
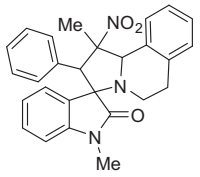
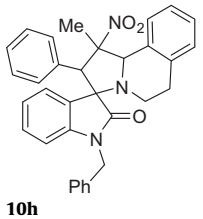
Fig. 4. ORTEP diagram of **10h**. Color available online.

crystallography (Fig. 4). The crystal structures analysis data are summarized in Table 3. Moreover, observation of a clear NOE between the $CHNO_2$ proton and H_a of **10a** in the differential NOE experiment further confirmed this stereochemistry.

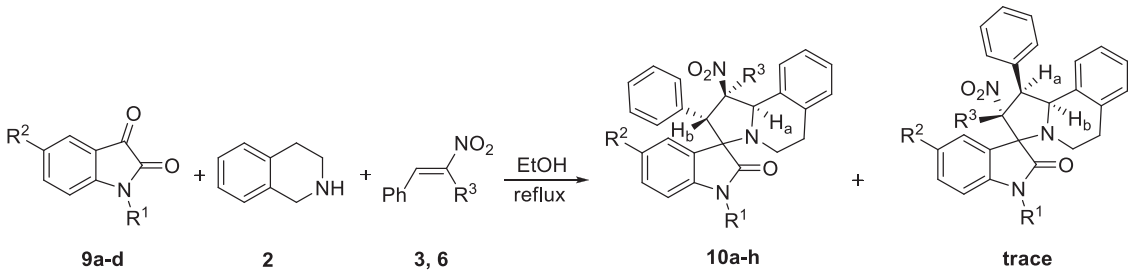
Notably, when 5-nitroisatin **11** and 1,2,3,4-tetrahydroisoquinoline **2** was treated with **3** or **6**, the expected spiro compounds were not formed and only 67:33 mixtures of inseparable iminium salts *(Z)*-**12** and *(E)*-**12** were collected, respectively (Scheme 5). The presence of a molecular ion peak at *m/z* 325 (M^+) in the mass spectrum of **12** confirmed the formation of the iminium salt. The geometries of the *Z*- and *E*-isomers of **12** were determined based on ^{1}H NMR chemical shift. A singlet at δ 4.96 ppm, attributed to the benzylic proton of (*Z*)-**12**, appeared at lower field compared to *(E)*-**12** (δ 4.92 ppm), due to a deshielding effect of the carbonyl group of the oxindole ring.

Given the large number of commercially available isatins and β-nitrostyrenes, the present method should be applicable to the synthesis of libraries with high diversity. We expect this method will find extensive application in

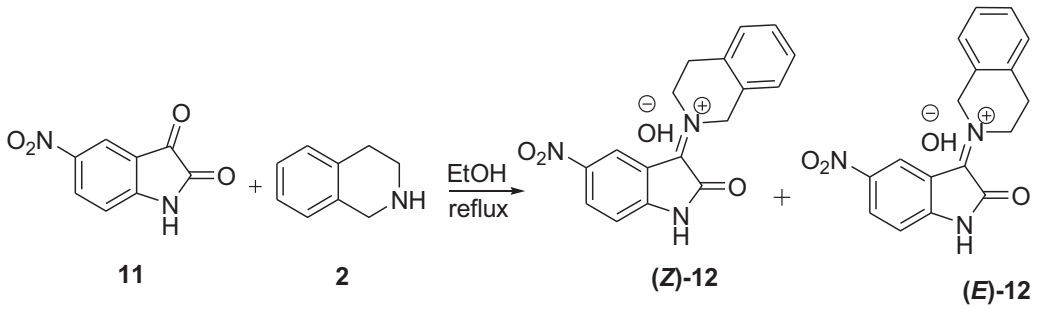
Table 2
Synthesis of spiroindolizidines **10a–h.**

Entry	R^1	R^2	R^3	Product	Yield[a] (%)
1	H	H	H	 **10a**	82
2	H	Br	H	 **10b**	84
3	Me	H	H	 **10c**	85
4	$PhCH_2$	H	H	 **10d**	89
5	H	H	Me	 **10e**	82
6	H	Br	Me	 **10f**	91
7	Me	H	Me	 **10g**	92
8	$PhCH_2$	H	Me	 **10h**	84

[a] Isolated yield.



Scheme 4. Regioselective synthesis of spiroindolizidines **10a**–**h**.



Scheme 5. Preparation of iminium salt **12**.

Table 3
Crystallographic data.

	4d	**10h**
Formula	$C_{27}H_{22}N_2O_5$	$C_{33}H_{29}N_3O_3$
M	454.47	515.59
Crystal size (mm)	0.40 × 0.15 × 0.10	0.40 × 0.25 × 0.15
Color	Yellow	Cream
a (Å)	9.4522 (7)	9.2205 (10)
b (Å)	11.2223 (10)	23.370 (3)
c (Å)	11.8315 (10)	12.7620 (13)
α (°)	108.037 (7)	90
β (°)	92.376 (7)	102.478 (8)
γ (°)	102.972 (7)	90
V (A^3)	2685.0 (5)	2685.0 (5)
λ (Å)	0.71073	0.71073
ρ_{calc} ($g\,cm^{-3}$)	1.307	1.276
μ (mm^{-1})	0.091	0.083
Z	2	4
Crystal system/space group	Triclinic/$P\bar{1}$	Monoclinic/$P2_1a$
Reflections collected	13014	19841
Reflections unique/R_{merge}	6165/0.0434	7238/0.1251
Reflection observed [$I \geq 2\,\sigma(I)$]	3843	3327
Refined parameter	307	352
R_1 (observed data)	0.1203	0.1931
wR_2 (all data)	0.1617	0.2707
Flack parameter	–	–
Max./min. residual electron density	0.23/–0.23	0.25/–0.32
CCDC	836 574	784 682

the field of drug discovery, combinatorial chemistry, and diversity-oriented synthesis.

3. Conclusion

In summary, we have developed a simple and convenient synthetic route for the construction of functionalized spiroindolizidines via a 1,3-dipolar cycloaddition reaction in which the 1,3-dipoles generated by 1,5-prototropic shift is reacted with β-nitrostyrenes as dipolaraphile. This afforded the anticipated cycloadducts in excellent yields with high regio- and stereoselectivity. The major adduct formed with isatin derivatives and the only adduct formed with ninhydrin are all in good agreement with the regio- and stereochemistry of the 1,3-dipolar cycloaddition.

4. Experimental

4.1. General procedure

A mixture of ninhydrin (0.178 g, 1 mmol) or isatin (0.147 g, 1 mmol), 1,2,3,4-tetrahydroisoquinoline (0.133 g, 1 mmol), and *trans*-β-nitrostyrene (0.149 g, 1 mmol) in ethanol (10 mL) was stirred at reflux for 2–3 h. After completion of the reaction, as indicated by TLC, the solid was separated by filtration, washed with ethanol (3 × 5), and the pure cycloadducts were obtained by recrystallization from ethanol.

4.1.1. 1′-Nitro-2′-phenyl-2′,5′,6′,10b′-tetrahydro-1′H-spiro[indene-2,3′-pyrrolo[2,1-a]isoquinoline]-1,3-dione (**4a**, $C_{26}H_{20}N_2O_4$)

Yellow solid; yield: 0.390 g (92%); M.p.: 187–189 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.64–2.75 (m, 2H, indolizine), 2.94–3.00 (m, 2H, indolizine), 4.47 (d, 1H, benzylic, *J* = 5.2 Hz), 5.61 (d, 1H, N–CH, *J* = 6.8 Hz), 6.56 (dd, 1H, $CHNO_2$, *J* = 7.2 Hz, 5.2 Hz), 7.16–8.05 (m, 13H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.6, 43.5, 57.9, 64.8, 77.8, 92.3, 123.1, 123.8, 125.3, 126.2, 127.4, 128.6, 129.0, 129.2, 129.4, 132.8, 133.8, 134.9, 137.6, 138.0, 141.1, 141.6, 198.3,

201.1; IR (KBr): $\bar{\nu}$ = 1752, 1708, 1556, 1377 cm^{-1}; anal. calcd. For $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60; found: C, 73.68; H, 4.79; N, 6.43.

*4.1.2. 1′-Nitro-2′-phenyl-2′,5′,6′,10b′-tetrahydro-1′H-spiro[indoline-3,3′-pyrrolo[2,1-a]isoquinolin]-2-one (**10a**, $C_{25}H_{21}N_3O_3$)*

Cream solid; yield: 0.337 g (82%); M.p.: 203–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66–2.81 (m, 3H, indolizine), 3.14 (m, 1H, indolizine), 4.52 (d, 1H, *J* = 4.8 Hz, benzylic), 5.86 (d, 1H, *J* = 6.8 Hz, N–CH), 6.14 (dd, 1H, *J* = 7.2, 4.8 Hz, $CHNO_2$), 6.72 (d, 1H, *J* = 8 Hz, Ar–H), 7.06–7.34 (m, 11H, Ar–H), 7.72 (d, 1H, *J* = 7.2 Hz, Ar–H), 10.18 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9, 42.5, 60.3, 63.6, 75.6, 91.7, 109.7, 123.6, 124.5, 124.9, 126.1, 127.1, 127.3, 128.1, 128.4, 128.6, 129.3, 130.0, 132.7, 133.7, 135.1, 141.4, 176.8; IR (KBr): $\bar{\nu}$ = 3316, 1720, 1552, 1322 cm^{-1}; anal. calcd. For $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.14; N, 10.21; found: C, 73.09; H, 5.06; N, 10.27.

Acknowledgements

The authors acknowledge the University of Mazandaran for financial support of this research.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.crci.2013.06.003.

The X-ray crystal structures data of **4d** and **10h** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 836574 and 784682 respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

References

[1] (a) O. Tsuge, S. Kanemasa, A.R. Katritzky, Adv. Heterocycl. Chem. Acad. 45 (1989) 231;
(b) A. Dömling, I. Ugi, Angew. Chem. Int. Ed. 39 (2000) 3169;
(c) C. Hulme, V. Gore, Curr. Med. Chem. 10 (2003) 51;
(d) J.P. Zhu, Eur. J. Org. Chem. 7 (2003) 1133;
(e) A. Ulaczyk-Lesanko, D.G. Hall, Curr. Opin. Chem. Biol. 9 (2005) 266;
(f) N. Isambert, R. Lavilla, Chem. Eur. J. 14 (2008) 8444;
(g) B. Ganem, Acc. Chem. Res. 42 (2009) 463.
[2] L. Weber, Drug Discov. Today 7 (2002) 143.
[3] (a) K. Nakanishi, D.H.B. Barton, Comprehensive Natural Products Chemistry, Elsevier Science, Oxford, 1999, Vol. 4, p. 25;
(b) P.M. Dewick, Medicinal Natural Products, Wiley, 1998, p. 289;
(c) J.P. Michael, Nat. Prod. Rep. 22 (2005) 603;
(d) J.P. Michael, Nat. Prod. Rep. 24 (2007) 191;
(e) J.P. Michael, Nat. Prod. Rep. 25 (2008) 139.
[4] J.S. Bindra, R.H.F. Manske, The Alkaloids, Academic Press, New York, 1973, Vol. 14, p. 84.

For reviews

[5] (a) C.V. Galliford, K.A. Scheidt, Angew. Chem. Int. Ed. 46 (2007) 8748;
(b) C. Marti, E.M. Carreira, Eur. J. Org. Chem. 12 (2003) 2209.
[6] (a) S.M. Allin, S.N. Gaskell, J.M.R. Towler, P.C. Bulman Page, B. Saha, M.J. McKenzie, W.P. Martin, J. Org. Chem. 72 (2007) 8972;
(b) K.R. Bailey, A.J. Ellis, R. Reiss, T.J. Snape, N.J. Turner, Chem. Commun. (2007) 3640;
(c) R.S. Kumar, S. Perumal, Tetrahedron Lett. 48 (2007) 7164;
(d) A. Kapat, P.S. Kumar, S. Baskaran, Beilstein J. Org. Chem. 3 (2007) 49;
(e) H. Liu, G. Dou, D. Shi, J. Comb. Chem. 12 (2010) 633;
(f) S.J.T. Rezaei, M.R. Nabid, A. Yari, S.W. Ng, Ultrason. Sonochem. 18 (2011) 49;
(g) M.N. Cheng, H. Wang, L.Z. Gong, Org. Lett. 13 (2011) 2418.
[7] A. Longeon, M. Guyot, J. Vacelet, Experentia 46 (1990) 548.
[8] V. Jager, R. Muller, T. Liebold, M. Hein, M. Schwarz, M. Fengler, L. Jaroskova, M. Patzel, P.Y. Le Roy, Bull. Soc. Chim. Belg. 103 (1994) 491.
[9] (a) H. Pellissier, Tetrahedron 63 (2007) 3235;
(b) T.M.V.D. Pinho e Melo, Eur. J. Org. Chem. 2006 (2006) 2873;
(c) G. Pandey, P. Banerjee, S.R. Gadre, Chem. Rev. 106 (2006) 4484;
(d) K. Rück-Braun, T.H.E. Freysoldt, F. Wierschem, Chem. Soc. Rev. 34 (2005) 507;
(e) S. Kanemasa, Synlett 9 (2002) 1371.
[10] (a) L.M. Harwood, R.J. Vickers, A. Padwa, W.H. Pearson, Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, John Wiley & Sons, New York, 2002, p. 169;
(b) K.V. Gothelf, S. Kobaya-Shi, K.A. Jorgensen, Cycloaddition Reactions in Organic Synthesis, Wiley-VCH, Weinheim, Germany, 2002, p. 211;
(c) S. Karlsson, H.E. Högberg, Org. Prep. Proced. Int. 33 (2001) 103;
(d) K.V. Gothelf, K.A. Jørgensen, Chem. Rev. 98 (1998) 863;
(e) R. Sustmann, W. Sicking, R. Huisgen, J. Org. Chem. 58 (1993) 82;
(f) A. Padwa, 1,3-Dipolar Cycloaddition Chemistry, John Wiley & Sons, New York, 1984, p. 277;
(g) H.A. Dondas, R. Grigg, W.S. MacLachlan, D.T. MacPherson, J. Markandu, V. Sridharan, S. Suganthan, Tetrahedron Lett. 41 (2000) 967.
[11] (a) M. Nyerges, L. Balázs, I. Kádas, I. Bitter, I. Kövesdi, L. Tőke, Tetrahedron 51 (1995) 6783;
(b) M. Nyerges, M. Rudas, G. Toth, B. Herenyi, I. Kádas, I. Bitter, L. Tőke, Tetrahedron 51 (1995) 13321;
(c) M. Ayerbe, F.P. Cossío, Tetrahedron Lett. 36 (1995) 4447;
(d) M. Ayerbe, I. Morao, A. Arrieta, A. Linden, F.P. Cossío, Tetrahedron Lett. 37 (1996) 2311;
(e) M. Ayerbe, A. Arrieta, F.P. Cossío, A. Linden, J. Org. Chem. 63 (1998) 1795.
[12] (a) M. Poornachandran, R. Muruganantham, R. Raghunathan, Synth. Commun. 36 (2006) 141;
(b) M. Poornachandran, R. Raghunathan, Synth. Commun. 37 (2007) 2507;
(c) S.M. Rajesh, S. Perumal, J.C. Menéndez, P. Yogeeswaric, D. Sriram, Med. Chem. Commun. 2 (2011) 626.
[13] (a) C. Najera, J.M. Sansano, Curr. Org. Chem. 7 (2003) 1105;
(b) I. Coldham, R. Hufton, Chem. Rev. 105 (2005) 2765.
[14] (a) H. Ardill, M.J.R. Dorrity, R. Grigg, M.S. Leon-Ling, J.F. Malone, V. Sridharan, S. Thianpatanagul, Tetrahedron 46 (1990) 6433;
(b) Y. Sarrafi, M. Hamzehlouian, K. Alimohammadi, H.R. Khavasi, Tetrahedron Lett. 51 (2010) 4734;
(c) J. Jayashankaran, R.D.R.S. Manian, R. Raghunathan, Arkivoc xi (2005) 32;
(d) J. Jayashankaran, R.D.R.S. Manian, R. Venkatesan, R. Raghunathan, Tetrahedron 61 (2005) 5595;
(e) R.R. Kumar, S. Perumal, Tetrahedron 63 (2007) 12220.
[15] K. Alimohammadi, Y. Sarrafi, M. Tajbakhsh, S. Yeganegi, M. Hamzehloueian, Tetrahedron 67 (2011) 1589.