Tetrahedron Letters 51 (2010) 6822–6824

Contents lists available at ScienceDirect

Tetrahedron Letters

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

The first example of an intramolecular Diels–Alder furan (IMDAF) reaction of iminium salts and its application in a short and simple synthesis of the isoindolo[1,2-*a*]isoquinoline core of the jamtine and hirsutine alkaloids

Fedor I. Zubkov [a,*], Julya D. Ershova [a], Vladimir P. Zaytsev [a], Mykola D. Obushak [b], Vasyl S. Matiychuk [b], Ekaterina A. Sokolova [a], Victor N. Khrustalev [c], Alexey V. Varlamov [a]

[a] Organic Chemistry Department, Peoples' Friendship University of Russia, 6 Miklukho-Maklaya St., Moscow 117198, Russian Federation
[b] Department of Organic Chemistry, Ivan Franko National University of Lviv, 6 Kyryla i Mefodiya St., Lviv 79005, Ukraine
[c] Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov St., Moscow 119991, Russian Federation

ARTICLE INFO

Article history:
Received 20 August 2010
Revised 24 September 2010
Accepted 8 October 2010
Available online 16 October 2010

Keywords:
Intramolecular Diels–Alder furan reaction
IMDAF
Alkaloids jamtine
Hirsutine
Isoindolo[1,2-*a*]isoquinoline

ABSTRACT

1-(2-Furyl)-3,4-dihydroisoquinolines, easily prepared from readily available phenethylamines, undergo tandem alkylation/[4+2]-cycloaddition with allyl halides. The reaction proceeds via 2-allyl-1-furyl-3,4-dihydroisoquinolinium salt formation and subsequent intramolecular *exo*-Diels–Alder reaction of furan with the allyl fragment (IMDAF reaction). The adducts formed include the basic structural element of the isoindolo[1,2-*a*]isoquinoline alkaloids jamtine and hirsutine.

The isoindolo[1,2-*a*]isoquinoline skeleton is a common heterocyclic fragment produced by various medicinal plants. For example, the shrubs *Cocculus hirsutus* (L.) and *Berberis darwinii* Hook contain the alkaloids jamtine[1] and hirsutine,[2] respectively. Due to their biological properties, both these alkaloids are the focus of synthetic organic chemistry. The first synthesis of (±)-jamtine via a tandem thionium/*N*-acyliminium ion cyclization of a difficult to prepare enamido sulfoxide precursor was reported by Padwa's research group in 2002.[3] Simpkins[4] later proposed the synthesis of (+)-jamtine using difficult to access chiral lithium amide bases.

Following our studies on intramolecular Diels–Alder furan (IMDAF) reactions,[5] we recently reported a novel approach to the construction of the isoindolo[1,2-*a*]isoquinoline skeleton from readily available 1-(2-furyl)tetrahydroisoquinolines **1**,[6] in which the IMDAF reaction was used as the key step of this process. Reduction of the amide group of **4** for assembling the jamtine core became a problematic task because it requires a strong base such as a metal hydride which causes undesirable side processes. To avoid this problem we first had to alkylate the same precursor **1** with allyl bromide followed by thermal [4+2]-cycloaddition of the allyl fragment to the furan ring in the intermediate *N*-alkyl derivative **2** to obtain the desired isoindolo[1,2-*a*]isoquinoline **3**.

Surprisingly, it was found that derivatives **2** did not undergo the intramolecular Diels–Alder cyclization even at 160 °C,[7] or in the presence of various Lewis acid catalysts (Scheme 1).

An elegant solution to this problem was found unexpectedly by studying the N-alkylation reaction of 1-furyl-3,4-dihydroisoquinoline[6,8] (**5a**) and allyl bromide at room temperature in acetonitrile. To our delight the alkylation proceeded in satisfactory yield affording the stable adduct **7a**.[9]

Evidently, the iminium salt **6a**, which was formed during the first stage, underwent a spontaneous IMDAF reaction to form the target isoindolo[1,2-*a*]isoquinolinium salts **7a** in one pot (Scheme 2).

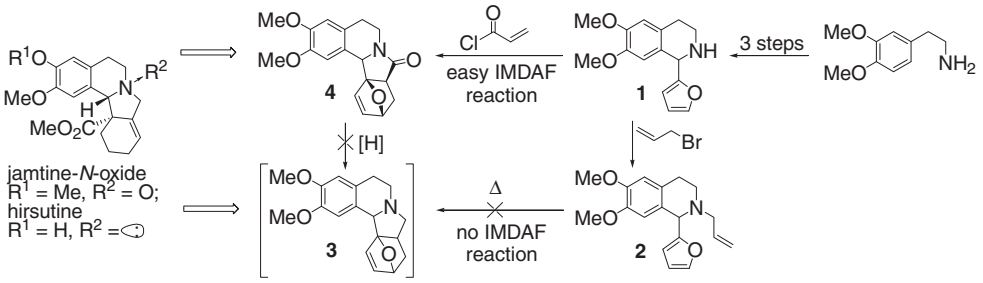
It is worth noting that the cycloaddition shows high diastereoselectivity, giving only the *exo*-adduct **7a**.

To the best our knowledge, this is the first example of the successful implementation of an IMDAF reaction of furfurylamines containing a positively charged nitrogen atom. There are only a few early reports on the possibility of intramolecular cyclization of quaternary ammonium *N*-furfuryl-*N*-allyliminium salts.[10] Moreover, the chemical structures of the synthesized adducts were not confirmed by spectral methods.

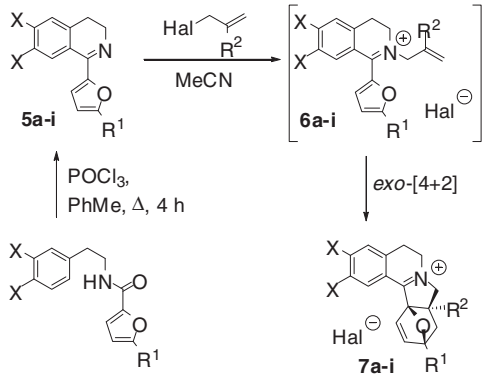
Taking into consideration that intramolecular [4+2]-cycloadditions of *N*-alkenylfurfurylamines are extremely sensitive to steric and electronic effects in the dienophile moiety,[4] the influence of the nature of the substituents on the diene and in the dienophile

* Corresponding author. Tel./fax: +7 495 955 0779.
E-mail address: fzubkov@sci.pfu.edu.ru (F.I. Zubkov).

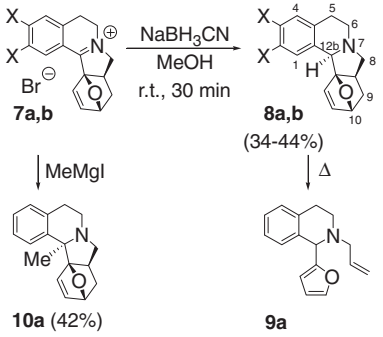
0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.10.046



Scheme 1.



Scheme 2.



Scheme 3.

moiety of intermediate **6** on the reaction conditions, time and yield were investigated (Table 1).

It was found that both donor and acceptor substituents (R^2) on the allylic moiety impeded the Diels–Alder reaction and reduced appreciably the yields of the desired salts **7c–f** (considerable polymerization occurred in these cases). This can be explained by the steric hindrance. It was thus necessary to boil intermediates **6** for 2–5 h in acetonitrile or isopropanol.

Most probably, in view of the steric hindrance, the tandem alkylation/[4+2]-cycloaddition was not successful in the case of the reactions of **5a**,**b** with cinnamoyl chloride. Instead *N*-alkyl derivatives similar to **6** were isolated.

The influence of substituent R^1 was less dramatic. 1-Furyl-3,4-dihydroisoquinolines **5g–i**, with both donor and acceptor substituents (R^1 = H, Ar, Hal) on the furan core underwent the IMDAF reaction leading to epoxyisoindolo[1,2-*a*]isoquinolinium salts **7** in good yields.

It is interesting to note that reduction of salts **7a**,**b** using sodium cyanoborohydride led to isoindolo[1,2-*a*]isoquinolines **8a**,**b** in moderate yields (Scheme 3), while the use of sodium borohydride gave rise to unsatisfactory results ($LiAlH_4$ was not used in view of the low solubility of the salts in ethers). Hydrogenation products **7** proved to be unstable to heating (140 °C) and underwent retrodiene decomposition to form *N*-allylamines **9** (detected by LC–MS).

Treatment of salts **7** with excess of Grignard reagent allowed introduction of an alkyl radical at the 12b-position of the jamtine core (for example, compound **10a** in Scheme 3).

Table 1
Yields and melting points of hexahydro-10,12a-epoxyisoindolo[1,2-*a*]isoquinolinium salts **7**

Product	X	Hal	R^1	R^2	Mp[a] (°C)	Yield (%)
7a	H	Br	H	H	161–162	59
7b	OMe	Br	H	H	159–161	54
7c	H	I	H	Me	178–180	17
7d	OMe	I	H	Me	184–185	10
7e	H	I	H	Cl	182–183	13
7f	OMe	I	H	Cl	176–178	11
7g	H	Br	Br	H	109–110	55
7h	OMe	Br	Br	H	141	86
7i	H	Br	2-$NO_2C_6H_4$	H	170–172	22

[a] All salts melt with decomposition; recrystallization of the salts was accomplished from an EtOAc/EtOH mixture.

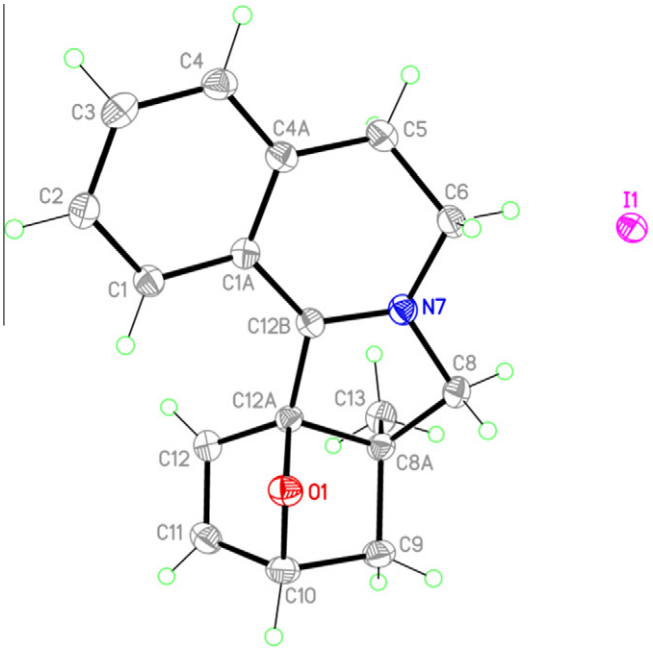


Figure 1. Molecular structure of iodide **7c**. Thermal ellipsoids are shown at the 50% probability level.

The NMR data of 8a-R^2-substituted adducts **7c–f** were not sufficient to elucidate unambiguously their structures. In particular, NMR spectroscopy was not able to determine the orientation (*exo*- or *endo*-) of the 8a-Me (8a-Cl) group relative to the oxygen bridge. This problem was solved by X-ray diffraction analysis of adduct **7c** (Fig. 1).[11]

The cation of compound **7c** possesses three asymmetric centers at the C8a, C10 and C12a carbon atoms and can potentially exist as four diastereomers. Single crystal X-ray data revealed that the crystal of **7c** was racemic and consists of enantiomeric pairs with the following relative configurations of the stereogenic centers: *rac*-8a*R**,10*R**,12a*R**.

In summary, we have developed a new strategy for the synthesis of hexahydro-10,12a-epoxyisoindolo[1,2-*a*]isoquinolinium halides, which were easily prepared by a one-pot N-alkylation/intramolecular Diels–Alder cascade from readily available allyl halides and 1-(2-furyl)dihydroisoquinolines. This strategy is intended to permit future access to the alkaloids nuevamine, jamtine, hirsutine and their derivatives by introducing appropriate substituents at the beginning of the syntheses.

Acknowledgements

The authors are grateful to the Russian Foundation for Basic Research for the financial support of this work (Grant No. 11-03-90416 Укр_ф_а) and to Professor Vladimir V. Kouznetsov for invaluable assistance in preparing this Letter.

References and notes

1. (±)-Jamtine isolation: (a) Ahmad, V. U.; Rahman, A.; Rasheed, T.; Rehman, H. *Heterocycles* **1987**, *26*, 1251–1255; (b) Ahmad, V. U.; Iqbal, S. *Phytochemistry* **1993**, *3*, 735–736; (c) Ahmad, V. U.; Iqbal, S. *Nat. Prod. Lett.* **1993**, *2*, 105–109.
2. (±)-Hirsutine isolation: Rasheed, T.; Khan, M. N.; Zhadi, S. S.; Durrani, S. J. *Nat. Prod.* **1991**, *54*, 582–584.
3. (a) Padwa, A.; Danca, M. D. *Org. Lett.* **2002**, *4*, 715–717; (b) Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.* **2003**, *68*, 929–941.
4. Simpkins, N. S.; Gill, C. D. *Org. Lett.* **2003**, *5*, 535–537.
5. Recent IMDAF review: Zubkov, F. I.; Nikitina, E. V.; Turchin, K. F.; Safronova, A. A.; Borisov, R. S.; Varlamov, A. V. *Russ. Chem. Bull.* **2004**, *53*, 860–872.
6. IMDAF approach to alkaloids: Zubkov, F. I.; Ershova, J. D.; Orlova, A. A.; Zaytsev, V. P.; Nikitina, E. V.; Peregudov, A. S.; Gurbanov, A. V.; Borisov, R. S.; Khrustalev, V. N.; Maharramov, A. M.; Varlamov, A. V. *Tetrahedron* **2009**, *65*, 3789–3803.
7. (a) Choony, N.; Dadabhoy, A.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2017; (b) Choony, N.; Dadabhoy, A.; Sammes, P. G. *Chem. Commun.* **1997**, 513.
8. Horak, Y.; Matiychuk, V.; Lytvyn, R.; Obushak, M. *Visnyk Lviv Univ. Ser. Chem.* **2006**, *47*, 193–200.
9. *Synthesis of (8aR*,10R*,12aR*)-5,6,8,8a,9,10-hexahydro-10,12a-epoxyisoindolo[1,2-a]isoquinolinium bromide* **(7a)**. Allyl bromide (0.65 mL, 7.5 mmol) was added to a stirred solution of 1-furyl-3,4-dihydroisoquinoline (**5a**) (1.00 g, 5 mmol) in MeCN (25 mL). The reaction mixture was kept at room temperature for about 4 d (monitoring by TLC). On completion the solvent was removed under reduced pressure and the residue crystallized from EtOAc–EtOH to give 0.94 g of isoquinolinium bromide **7a** as pale-yellow prisms. Yield 59%, R_f = 0.5 (EtOAc–EtOH, 1:2); IR (KBr): 1638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.74 (dd, *J* = 8.1, *J* = 11.9 Hz, 1H, H-9_{endo}), 2.00 (ddd, *J* = 3.7, *J* = 4.4, *J* = 11.9 Hz, 1H, H-9_{exo}), 3.10 (ddd, *J* = 4.0, *J* = 6.2, *J* = 16.2 Hz, 1H, H-5B), 3.30 (dq, *J* = 3.7, *J* = 8.2 Hz, 1H, H-8a), 3.80 (ddd, *J* = 7.4, *J* = 14.5, *J* = 16.2 Hz, 1H, H-5A), 3.95 (dd, *J* = 8.0, *J* = 14.0 Hz, 1H, H-8B), 4.10 (ddd, *J* = 6.2, *J* = 14.5, *J* = 15.0 Hz, 1H, H-6B), 4.75 (ddd, *J* = 4.0, *J* = 7.4, *J* = 14.0 Hz, 1H, H-6A), 5.19 (dd, *J* = 8.6, *J* = 14.0 Hz, 1H, H-8A), 5.35 (dd, *J* = 1.7, *J* = 4.5 Hz, 1H, H-10), 6.57 (d, *J* = 1.7, *J* = 5.9 Hz, 1H, H-11), 6.99 (d, *J* = 5.9 Hz, 1H, H-12), 7.30 (t, *J* = 7.7 Hz, 1H, H-2), 7.42 (d, *J* = 7.7 Hz, 1H, H-4), 7.68 (dd, *J* = 1.3, *J* = 7.8 Hz, 1H, H-1), 7.71 (dt, *J* = 1.3, *J* = 7.7 Hz, 1H, H-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.6, 30.2, 42.2, 47.0, 63.7, 82.5, 96.4, 122.3, 128.1, 128.7, 130.4, 133.6, 136.6, 137.5, 138.0, 170.8. MS (EI, 70 eV): *m/z* (%) = 238 (15) $[M-Br]^+$, 208 (13), 189 (14), 165 (20), 128 (16), 115 (30), 108 (27), 95 (15), 81 (95), 79 (100), 59 (45), 43 (55). Anal. Calcd for $C_{16}H_{16}BrNO$: C, 60.39; H, 5.07; N, 4.40. Found: C, 60.21; H, 5.18; N, 4.27.
10. (a) Babayan, A. T.; Tagmazyan, K. T.; Mkrtchan, R. S. *Dokl. Akad. Nauk Arm. SSR Org. Khim.* **1972**, *55*, 224 [*Chem. Abstr.* **1973**, *79*, 92058]; (b) Tagmazyan, K. T.; Mkrtchan, R. S.; Babayan, A. T. *Arm. Khim. Zh.* **1974**, *27*, 957 [*Chem. Abstr.* **1975**, *82*, 111234]; (c) Tagmazyan, K. T.; Torosyan, G. O.; Mkrtchan, R. S.; Babayan, A. T. *Arm. Khim. Zh.* **1976**, *29*, 352 [*Chem. Abstr.* **1977**, *86*, 42746]; (d) Hernández, J. E.; Fernández, S.; Arias, G. *Synth. Commun.* **1988**, *18*, 2055.
11. Full crystallographic data of salt **7c**: Toze Flavien, A. A.; Ershova, J. D.; Obushak, M. D.; Zubkov, F. I.; Khrustalev, V. N. *Acta Crystallogr., Sect. E* **2010**, *66*, o1388–o1389. Crystallographic data for compound **7c** have been deposited with the Cambridge Crystallographic Data Centre. CCDC 781365 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).