Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

The intramolecular Diels–Alder vinylfuran (IMDAV) reaction: a short approach to aza-analogues of pinguisane-type sesquiterpenes

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ARTICLE INFO

Article history:
Received 12 March 2015
Revised 25 May 2015
Accepted 29 May 2015
Available online xxxx

Keywords:
Furan
[2+4] cycloaddition
Diels–Alder reaction
IMDAV
Furo[2,3-*f*]isoindoles
Pinguisane-type sesquiterpenes

ABSTRACT

The reaction of readily accessible (3-furyl)allylamines with maleic anhydride, followed by a domino sequence involving acylation/cycloaddition/proton shift steps, led to the formation of furo[2,3-*f*]-isoindoles—the aza-analogs of pinguisane-type sesquiterpenes. The key intramolecular Diels–Alder vinylfuran (IMDAV) reaction proceeded under mild conditions, with high levels of diastereoselectivity and satisfactory yields.

A large group of pinguisane-type sesquiterpenoids, possessing the indeno[5,6-*b*]furan core, are widely distributed in liverworts.[1] Compounds isolated from these plants show a broad and diverse spectrum of biological activities that include antidermatitis,[2] anti-cancer,[3] and antimicrobial[4] activities. Several representative examples of such compounds, with structures closest to the subject of this work, are shown in Figure 1.

It is well known that the introduction of an additional heteroatom into a drug-molecule can dramatically alter its biological activity. Thereby, this work was aimed at the development of a simple entry to aza-analogues of pinguisane-type sesquiterpenes.

The intramolecular Diels–Alder furan (IMDAF) reaction[5] is a powerful and useful tool for the synthesis of alkaloids and other natural and bioactive substances. The key step of such reactions is the [2+4] cycloaddition where the furan moiety plays the role of an internal diene (transformation **4** → **5**, Fig. 2). The related intramolecular cycloaddition, where a vinylfuran fragment acts as the internal diene—the intramolecular Diels–Alder vinylfuran (IMDAV) reactions (**7** → **8**),[6] are much less studied.

Unlike IMDAF, use of IMDAV allows preservation of the furan motif in the target molecules, making it possible to synthesize in one step furans, that are [*b*]annulated with six-membered rings. These benzo[*b*]furans (**9**, Fig. 2) are of ubiquitous structure in the plant kingdom.[7]

A literature survey showed that to date a very limited number of examples for the successful synthesis of benzofurans using the IMDAV reaction have been described.[7,8] Typically, this process (**7** → [**8**] → **9**, Fig. 2) requires high temperatures[8] (200–300 °C), which restricts the synthetic potential of this method. In some cases the reaction stops after formation of intermediate **8**[8e] or is complicated by the formation of isomeric mixtures.[8d] Allenes and alkynes[7e,9] can also perform as the dienophile in this type of transformation. Information about the synthesis of furo[2,3-*f*]isoindoles using the IMDAV reaction is nearly absent.[8f,10]

The present communication is aimed at the development of a simple approach to furo[2,3-*f*]isoindoles, based on the use of readily available compounds such as furylacroleins and aliphatic or aromatic amines.

Initially (3-furyl)allylamines **12a–l** were synthesized by the one-pot method,[11] shown in Scheme 1. Neither azomethines **11** nor allylamines **12** were isolated, and were used in the next step

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http://dx.doi.org/10.1016/j.tetlet.2015.05.115
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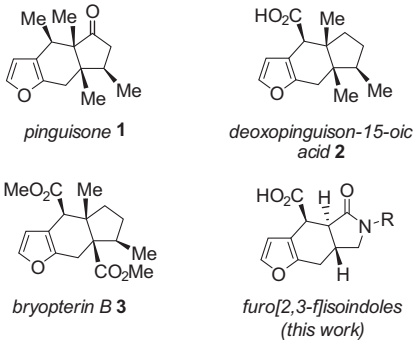


Figure 1. Representative examples of natural sesquiterpenes including the indeno[5,6-*b*]furan moiety **1**–**3**.

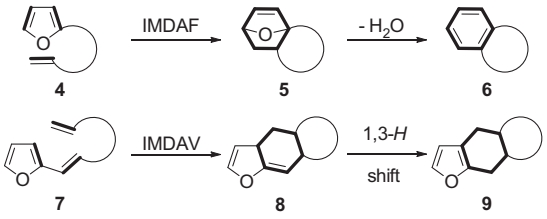


Figure 2. An overview of IMDAF and IMDAV approaches in synthesis.

without purification. Amines **12a**–**l** were acylated with an equimolar amount of maleic anhydride under moderate heating. This reaction did not stop at the N-acylation stage, and was followed by the IMDAV reaction of the intermediate maleic amides **13a**–**l**, and spontaneous prototropic tautomerism of adducts **14a**–**l**.[12] The described domino-cascade gave the target furo[2,3-*f*]isoindoles **15a**–**l** in good yields (Table 1) as single diastereoisomers. The relative arrangement of the substituents was established using compounds **15b**[13] (Fig. 3) and **15e**.[14]

The relatively low yield (40%) of allyl derivative **15b** (R^2 = Allyl) is postulated to be due to competitive side reactions of intermolecular and intramolecular cycloaddition of the allyl substituent.

A single crystal X-ray structure determination was carried out for compound **15b** (Fig. 3). The crystal was found to be centrosymmetric and its asymmetric part consisted of two independent molecules, A and B (ESI, Fig. S1), of same chirality and similar geometry. The only considerable difference between them was the conformation of the allyl group. The isoindole five-membered rings in both independent molecules adopt envelope conformations that are puckered on the C7a atom, whereas the six-membered rings are half-chair-puckered. The carboxyl hydrogen atoms were involved in strong hydrogen bond formation with

Table 1
Yields and melting points of the obtained furo[2,3-*f*]isoindoles **15**

Compound **15**	R^1	R^2	Mp (°C)	Yield[a] (%)
a	H	*i*-Pr	224.9–225.5	72
b	H	Allyl	186.9–187.5	40
c	H	Cyclopentyl	215.5–216.5	70
d	H	Bn	212–214	62
e	H	Ph	251–252	64
f	Me	Ph	234–235	61
g	Me	Bn	178.5–179	82
h	2-$CF_3C_6H_4$	4-$MeOC_6H_4$	250–251	74
i	2,4-$Cl_2C_6H_3$	2-FC_6H_4	293–294	69
j	2,4-$Cl_2C_6H_3$	Ph	247–248	72
k	2-ClC_6H_4	4-$MeOC_6H_4$	234–235	70
l	2-FC_6H_4	4-$MeOC_6H_4$	258–259	75

[a] All yields are based on the initial furylacroleins **10**.

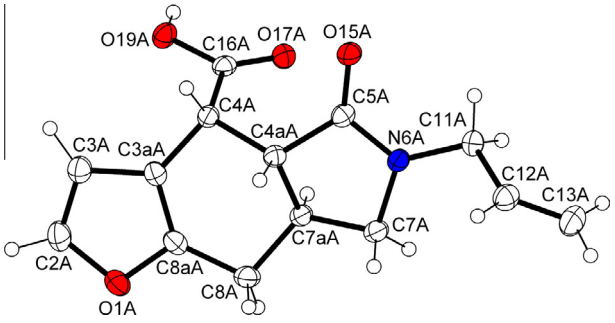


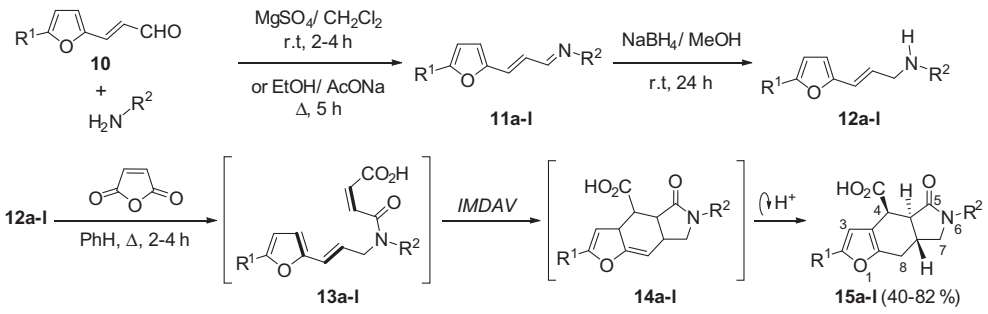
Figure 3. Molecular structure of one of two independent molecules of **15b**.[13] Molecule with (4*R*,4a*R*,7a*S*) absolute configuration is presented.

the O15 carbonyl atoms of neighboring molecules, giving rise to $(A...B...)_n$ chains.

In summary, we have developed a practical one-pot, three-step domino sequence for the construction of furans that are [*b*]-annulated with a perhydro isoindole ring, using inexpensive and readily available starting compounds. The use of maleic anhydride as the dienophile gave rise to furo[2,3-*f*]isoindoles from an IMDAV reaction. In contrast to existing methods, the IMDAV reaction was observed to proceed under rather mild reaction conditions, and with a high level of diastereoselectivity. Our synthetic groups aim to continue exploring the fruitful chemistry described herein by broadening the diversity of the initial dienes to 2-vinylthiophene, 2-vinylpyrrole, and 3-vinylindole moieties.

Acknowledgments

The authors are grateful to the Ukrainian State Fund for Fundamental Research (Grant No. F53.3/013) and the Russian



Scheme 1. Synthesis of initial 3-(furan-2-yl)prop-2-en-1-amines **12** and target furo[2,3-*f*]isoindoles **15**.

Foundation for Basic Research for the financial support (grants no. 13-03-90400 and 13-03-00105).

Supplementary data

Physicochemical properties, copies of ^{1}H and ^{13}C NMR spectra for compounds **15a–l** and the single crystal X-ray structure of molecule **15b** (Fig. S1). Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.115. These data include MOL files and InChiKeys of the most important compounds described in this article.

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11. The initial furylacrolein (R^1 = H) and (5-methylfuryl)acrolein (R^1 = Me) **10** are commercially available compounds; (5-arylfuryl)acroleins (R^1 = Ar) **10** were synthesized as described in the ESI.
Synthesis of 3-(furan-2-yl)prop-2-en-1-amines **12a–g**. To a stirred solution of amine (20 mmol) and the corresponding furylacrolein **10** (20 mmol) in CH_2Cl_2 (50 mL) was added powdered anhydrous $MgSO_4$ (4.8 g, 40 mmol) at rt. After ca. 4 h, the $MgSO_4$ was filtered off, washed with CH_2Cl_2 (2 × 20 mL), and the solution concentrated. The residue yellow oil was diluted with MeOH (40 mL), and $NaBH_4$ (1.1 g, 20 mmol) was added. The mixture was stirred vigorously at rt for 24 h, poured into H_2O (200 mL), and extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and directly used in the cycloaddition step.
Synthesis of amines **12h–l**. To a solution of the less reactive 5-arylfurylacroleins **10** (20 mmol) in EtOH (50 mL) was added the corresponding amine (20 mmol) and AcONa (1.64 g, 20 mmol). The mixture was heated at reflux for 5 h, then cooled to rt, and poured into H_2O (150 mL). The obtained brown crystals were filtered off, washed with H_2O, and dried in the air. The crude product was used directly in the reduction step as described above.
12. Synthesis of target furo[2,3-*f*]isoindoles **15**. The crude allylamine **12** was diluted with PhH (40 mL) and a solution of maleic anhydride (2.16 g, 22 mmol) in PhH (20 mL) was added. The resulting mixture was heated at reflux for 2–4 h (TLC monitoring) and then cooled to rt. The formed precipitate was filtered off, washed with PhH (10 mL), Et_2O (2 × 10 mL), and dried in air to give the title acids as white solids. Isolated compounds **15** could be recrystallized using EtOH, EtOAc or their mixture as solvent to obtain analytical samples for final characterization.
13. Crystallographic data for **15b**: empirical formula: $C_{14}H_{15}NO_4$, formula weight: 261.27 g/mol, crystal color, habit: colourless, needle, crystal system: monoclinic, space group: $P2_1/c$ (#14), a = 12.788(4), b = 10.140(3), c = 19.527(5) Å, β = 97.94(3)°, V = 2507.8(13) Å^3, T = 100(2) K, Z = 8, D_{calc} = 1.38 g/cm^3, $F(000)$ = 1104, diffractometer: Kuma KM4CCD, residuals: $R[F^2>2\sigma(F^2)]$, $wR(F^2)$: 0.0487, 0.1145. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1053271. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1233 336033 or e-mail deposit@ccdc.cam.ac.uk).
14. Detailed X-ray data for racemic furo[2,3-*f*]isoindole carboxylic acid **15e** were published earlier, see: Horak, Y. I.; Lytvyn, R. Z.; Zubkov, F. I.; Nikitina, E. V.; Homza, Y. V.; Lis, T.; Kinzhybalo, V.; Obushak, M. D. *Acta Cryst.* **2013**, *E69*, o273–o274.