Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 4357–4360
Tetrahedron Letters

An imino-Diels–Alder route to *meso*-2,6-disubstituted-4-piperidones

Ana-Belén García, Carlos Valdés and María-Paz Cabal*

Unidad asociada al CSIC, Instituto Universitario de Química Organometálica 'Enrique Moles', Universidad de Oviedo, 33071 Oviedo, Spain

Received 23 January 2004; revised 15 March 2004; accepted 31 March 2004

Abstract—A convenient stereoselective preparation of *meso*-2,6-disubstituted-4-piperidones has been developed by imino-Diels–Alder reaction of 2-amino-1,3-butadienes with imines in the presence of catalytic amount of $Cu(TfO)_2$.

1. Introduction

meso-Compounds are attractive prochiral materials that can be readily transformed into enantiomerically pure compounds through various desymmetrization processes.[1] Among them, *meso*-2,6-disubstituted-4-piperidones can be regarded a interesting frameworks as precursors of chiral biologically active and natural alkaloids.[2]

A research theme in our laboratory for many years has been the study of the imino-Diels–Alder reaction of 2-amino-1,3-butadienes with nonactivated aldimines. This method generally furnishes 4-piperidones with high stereoselectivity.[3] It has been previously shown that this cycloaddition can also be carried out asymmetrically to give adducts in very high enantiomeric excess (Fig. 1).[4] Moreover, this methodology has been applied to the synthesis of alkaloids,[5] structurally diverse pipecolic acid derivatives,[6] and most recently, to solid-phase organic synthesis.[7] However, the requirement of specific substituents on the diene ($R^1 = CH_2OR$, $R^2 = alkyl$) have been limiting the synthetic versatility of the reaction.[8]

In relation with an ongoing research project in our laboratory, we were interested in synthesizing 4-piperidones with different substituents at R^1 and $R^2 = H$. For this reason, we set out to investigate the optimal conditions for the imino-Diels–Alder reaction of 2-aminobutadienes unsubstituted at C-3, and the application of this methodology to the synthesis of *meso*-2,6-disubstituted-4-piperidones.

The synthesis of 3-unsubstituted-2-aminodienes **1** and **2** were carried out from commercially available starting reagents as propargyltriphenylphosphonium bromide, morpholine, or *N*-methylaniline and aromatic aldehydes by a modification of a previous procedure (Fig. 2).[9]

The synthetic sequence involves the preparation in situ of phosphorane **II** by reaction of β-enaminophosphonium salt **I** with sodium hexamethyldisilazide followed by a Wittig reaction with aromatic aldehydes affording

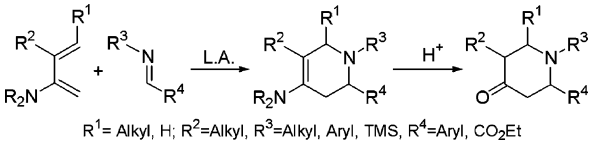


Figure 1. Imino-Diels–Alder reaction of 2-aminodienes.

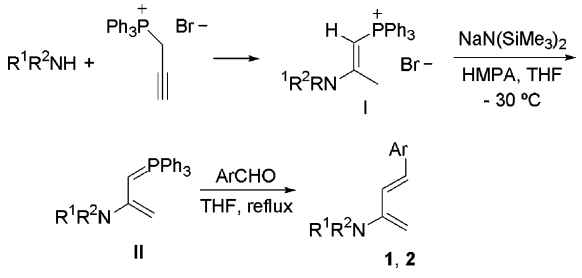


Figure 2. Synthesis of 2-aminodienes.

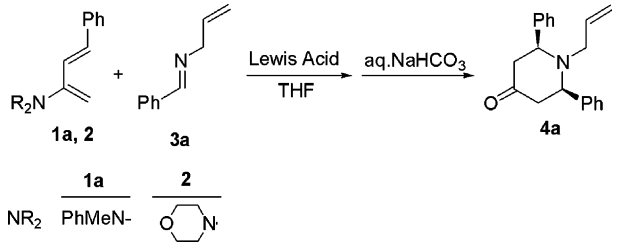
Keywords: Imino-Diels–Alder; Piperidones; *meso*-Compounds; $Cu(TfO)_2$.

* Corresponding author. Tel.: +34-985102990; fax: +34-985193446; e-mail: pcabal@fq.uniovi.es

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.195

the corresponding 2-aminodienes in good yield (80–98%).

We chose for our initial study 4-phenyl-2-amino-1,3-butadienes **1a** and **2**, which bear an aromatic amine (*N*-methylaniline) and an aliphatic amine (morpholine), respectively. The reaction of both dienes with *N*-allylbenzaldimine **3a**, was examined in the presence of a variety of Lewis acids known to activate imines in aza-Diels–Alder and Mannich type reactions[10] and under different reaction conditions (Scheme 1 and Table 1).

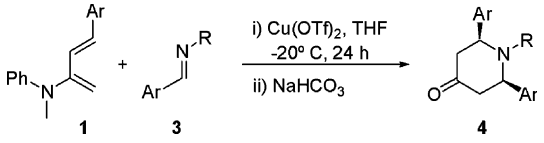


Scheme 1. Cycloaddition reaction of dienes **1a** and **2**.

The reaction afforded, after aqueous workup, the expected [4+2] cycloadduct **4a** with very high diastereoselectivity. Yields varied, depending on the nature of the Lewis acid and the diene. The *meso*-isomer was isolated in nearly pure diastereoisomeric form in all the reactions.[†] Diene **1a**, substituted with an aromatic amine furnished better yields than morpholine substituted diene **2** under the conditions examined (entries 1 vs 8 and 3 vs 10). Moreover, while both $Cu(OTf)_2$ and $Yb(OTf)_3$ promoted the cycloaddition, the best yields and diastereoselectivities were achieved with $Cu(OTf)_2$ as Lewis acid (entries 1 vs 3). In particular, excellent yield and diastereoselectivity was obtained when the cycloaddition was carried out with $Cu(OTf)_2$ at −20 °C (entry 6).

The high diastereoselectivity observed in the reaction is in agreement with an *endo* approach of the phenyl ring of the imine on a formal [4+2] cycloaddition. However, there is no evidence for a concerted mechanism, and in fact, Lewis–acid catalyzed imino-Diels–Alder reactions with electron-rich dienes have been proposed to occur in a stepwise fashion.[11]

This methodology, under these optimized conditions, was then extended to the synthesis of different substituted *meso*-piperidones **4**. These adducts could be readily obtained from reactions in which the aryl substituent of the diene is properly matched with the aryl imine **3**. The results are summarized in Table 2 (Scheme 2).



Scheme 2. Preparation of *meso*-piperidones **4**.

In most of the examples the 4-piperidones were obtained with excellent yields and diastereoselectivities. The reaction is fairly general regarding the structure of the aryl substituent (from the electron rich *p*-MeO–Ph to the electron poor *p*-F–Ph).

However, the outcome of the cycloaddition is greatly affected by the *N*-substituent of the imine; with *N*-aryl substituted imines we observed very low conversion, but still high diastereoselectivities. The 4-piperidones **4** are stable compounds under aqueous neutral conditions and can be purified by flash chromatography on silica gel. However, in a few cases (**4c**, R = Bn) we detected isomerization to the *trans* isomer (probably via a reversible *retro*-Michael ring opening-Michael ring closure sequence) during the chromatography, lowering the overall yield of the *cis* isomer.

Table 1. Synthesis of piperidone **4a** under different reaction conditions

Entry	Diene	Lewis acid (%mol)	*T* (°C)	Yield[a] (%)	De[b] (%)
1	**1a**	$Cu(OTf)_2$ (20)	Rt	60	93
2	**1a**	$CuClO_4{\cdot}CH_3CN$ (20)	Rt	46	93
3	**1a**	$Yb(OTf)_3$ (20)	Rt	53	91
4	**1a**	$Sc(OTf)_3$ (20)	Rt	39	90
5	**1a**	$ZnCl_2$ (100)	Rt	<10	—[c]
6	**1a**	$Cu(OTf)_2$ (20)	−20	90	94
7	**1a**	$Yb(OTf)_3$ (20)	−20	74	94
8	**2**	$Cu(OTf)_2$ (20)	Rt	33	93
9	**2**	$CuClO_4{\cdot}CH_3CN$ (20)	Rt	25	92
10	**2**	$Yb(OTf)_3$ (20)	Rt	30	92
11	**2**	$Yb(OTf)_3$ (20)	50	Traces	—[c]
12	**2**	$ZnCl_2$ (100)	Rt	<10	—[c]

[a] After chromatographic purification.
[b] Determined by ^1H NMR on the reaction crude.
[c] Not determined.

Table 2. Preparation of *meso*-2,6-diaryl-4-piperidones **4**

Compound **4**	Ar	R	De[a] (%)	Yield[b] (%)
a	Ph	Allyl	94	90
b	Ph	Butyl	>99	87
c	Ph	Bn	>99	55
d	Ph	Ph	96	20
e	Ph	*p*-MeO–Ph	96	15
f	*p*-MeO–Ph	Allyl	96	79
g	*p*-MeO–Ph	Butyl	>99	73
h	*o*-Br–Ph	Allyl	>99	89
i	*o*-Br–Ph	Butyl	>99	85
j	*p*-FPh	Allyl	>99	80
k	*p*-F–Ph	Butyl	>99	73

[a] Determined by ^1H NMR on the crude reaction mixture.
[b] Isolated yield of the *meso*-diastereomer after chromatographic purification.

[†] The *cis* arrangement of the substituents at positions 2 and 6 was deduced from the analysis of the ^1H NMR spectra and NOESY experiments.

In conclusion, we have described a very efficient method for the stereoselective synthesis of *meso*-2,6-disubstituted-4-piperidones by imino-Diels–Alder reaction of 3-unsubstituted 2-aminodienes. These compounds can be interesting starting materials for the preparation of enantiopure piperidine derivatives upon desymmetrization processes that are now being investigated and will be reported in due course.

2. Typical experimental procedure for the preparation of 4-aryl-2-amino-1,3-butadienes 1 and 2

The secondary amine (17 mmol) was added to a solution of propargyltriphenylphosphonium bromide (15 mmol) in Cl_2CH_2 (75 mL) and the solution was stirred at room temperature for 1.5 h. After the partial evaporation of the solvent, the resulting solution was added dropwise to ethyl acetate forming the crystalline β-enaminophosphonium salt that was filtered off and dry under vacuum to be used on the next step. To a suspension of β-enaminophosphonium salt (20 mmol) in anhydrous THF (75 mL) at −60 °C and under N_2, was added $NaN(SiMe_3)_2$ (1.3 equiv, 2 M in THF). The reaction mixture was stirred for 4 h, then the cold bath was removed, and the solution was allowed to reach room temperature (deep orange color was observed). Anhydrous HMPTA (1 equiv) was added at room temperature and after 30 min the reaction mixture was cooled at −30 °C. A solution of aldehyde (1.3 equiv) in anhydrous THF (15 mL) was added dropwise in a short time (deep orange color disappeared) and the mixture was keep at −30 °C. After 1 h, the cold bath was removed and the solution was allowed to reach room temperature followed by heating at 60 °C during 12 h. The solvents were removed under N_2 at reduced pressure and a gummy solid was obtained. Anhydrous hexane (60 mL) was added to the solid and allowed to stir for few minutes, the solid was filtered off under N_2, and washed again with dry hexane (2×25 mL). The solution was concentrated under N_2 at reduced pressure (25 mL) and allowed to stand overnight at −20 °C (solid precipitated was observed on the bottom flask). The solution was transferred under N_2, vía cannula, to a flask. After evaporation of the solvents at reduced pressure and under N_2, the 2-aminodiene was obtained mixed with some HMPTA, which was distilled at high vacuum (10^{-6} Torr) at room temperature giving the 4-aryl-2-aminodienes **1** or **2** as a yellow oil that can be used without any further purification. Compound **1a**: yellow oil (98%).

2.1. Selected spectroscopic data for compound 1a

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.21 (3H, s), 4.90 (1H, s), 5.14 (1H, s), 6.67 (2H, s), 6.82–6.96 (3H, m), 7.20–7.38 (7H, m) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 40.1 (CH_3), 106.4 (CH_2), 117.6 (2C, CH), 119.3 (CH), 126.6 (2C, CH), 126.9 (CH), 127.6 (CH), 128.4 (2C, CH), 128.7 (2C, CH), 130.4 (CH), 136.8 (C), 148.8 (C), 151.9 (C) ppm.

3. Typical experimental procedure for the synthesis of *meso*-2,6-disubstituted-4-piperidones 4

The Lewis acid (0.2 mmol) was placed under N_2 into a flame-dried Schlenk tube. Freshly distilled anhydrous THF (5 mL) was added with a syringe under N_2 and the resulting solution was stirred for 5 min at room temperature. The solution was treated with imine **2** (1 mmol) and stirred for 10 min. Finally, a solution of the diene **1** (1 mmol) in THF (10 mL) was added dropwise during 1 h. The reaction mixture was stirred at −20 °C for 24 h, quenched with $NaHCO_3$ satd aqueous solution, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product purified by flash column chromatography (SiO_2, EtOAc–hexane 1:10) to afford the corresponding cycloadduct product **4**. Yellow oil. R_f (SiO_2, EtOAc–hexanes 1:10): **4a**, 0.31.

3.1. Selected spectroscopic data for compound 4a

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (2H, dd, $J = 12.8$ Hz, 2.3 Hz), 2.81 (2H, t, $J = 12.8$ Hz), 3.00 (2H, d, $J = 7.1$ Hz), 3.96 (2H, dd, $J = 12.8$ Hz, 2.3 Hz), 4.64 (1H, dd, $J = 17.1$ Hz, 2.0 Hz), 5.04 (1H, dd, $J = 10.2$ Hz, 2.0 Hz), 5.72–5.83 (1H, m), 7.30–7.49 (10H, m) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 50.8 (CH_2), 51.0 (CH_2), 64.4 (CH), 119.5 (CH_2), 127.2 (CH), 127.5 (CH), 128.6 (CH), 130.5 (CH), 142.4 (C), 207.1 (C=O) ppm.

Acknowledgements

This research was supported by Consejería de Educación y Cultura del Principado de Asturias (FICYT PC-CIS01-22) and Asturpharma S.A.

References and notes

1. For representative examples see: (a) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371; (b) Sugasawa, K.; Shindo, M.; Noguchi, H.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 7377; (c) Vaulont, I.; Gais, H.-J.; Reute, N.; Schmitz, E.; Ossenkamp, R. K. L. *Eur. J. Org. Chem.* **1998**, 805; (d) Goldspink, N. J.; Simpkins, N. S.; Beckmann, M. *Synlett* **1999**, 1292; (e) Takahata, H.; Ouchi, H.; Ichinose, M.; Nemoto, H. *Org. Lett.* **2002**; (f) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184.
2. (a) Struntz, G. M.; Findlay, J. A. In *Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 25, pp 89–193; (b) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1987; Vol. 31, pp 193–315; (c) Edwards, M. W.; Daly, J. W.; Myers, C. W. *J. Nat. Prod.* **1988**, *51*, 1188.
3. Barluenga, J.; Aznar, F.; Cabal, M. P.; Valdés, C. *J. Org. Chem.* **1993**, *58*, 3391.
4. Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M. P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805.

5. (a) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1999**, *64*, 3736; (b) Barluenga, J.; Aznar, F.; Mateos, C.; Valdés, C. *Org. Lett.* **2002**, *4*, 1971.
6. Barluenga, J.; Fernández, A.; Aznar, F.; Valdés, C. *Tetrahedron Lett.* **2002**, *43*, 8159.
7. Barluenga, J.; Aznar, F.; Mateos, C.; Valdés, C. *Org. Lett.* **2002**, *4*, 3667.
8. The presence of $R^2 \neq H$ is a requirement in most of the methods of synthesis of 2-aminodienes, see: Barluenga, J.; Aznar, F.; Liz, R.; Cabal, M.-P. *J. Chem. Soc., Chem. Commun.* **1985**, 1375.
9. (a) Merino, I. Ph. D. Thesis, University of Oviedo, 1992; (b) Barluenga, J.; Merino, I.; Palacios, F. *Tetrahedron Lett.* **1990**, *31*, 6713.
10. (a) Bromidge, S.; Wilson, P. C.; Whiting, A. *Tetrahedron Lett.* **1998**, *39*, 8905; (b) Kobayashi, S.; Kusakabe, K.-I.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220; (c) Jorgensen, K. A.; Hazell, R. G.; Saaby, S.; Yao, S. *Chem. Eur. J.* **2000**, *6*, 2435.
11. Hermitage, S.; Jay, D. A.; Whiting, A. *Tetrahedron Lett.* **2002**, *43*, 9633.