Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8983–8986
Tetrahedron Letters

Reductive opening of 2,7-dihydrodinaphthoxepine and thiepine: easy regioselective preparation of 2,2′-difunctionalised binaphthyls

Francisco Foubelo,* Benjamín Moreno and Miguel Yus

Departamento de Química Orgánica, Facultad de Ciencias and Instituto, de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

Received 24 September 2004; revised 8 October 2004; accepted 8 October 2004
Available online 22 October 2004

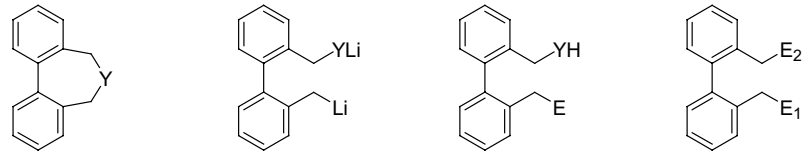
Dedicated to Professor Jean-Pierre Genêt on occasion of his 60th birthday

Abstract—The lithiation of 2,7-dihydrodinaphthoheteroepines (**5**) with 2.2 equiv of lithium naphthalenide in THF at −78 °C gives dianionic intermediates **8**, which by reaction with different electrophiles [H_2O, D_2O, ^tBuCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$] at the same temperature, followed by hydrolysis, leads to unsymmetrically 2,2′-disubstituted binaphthyls **6**. When the lithiation is performed with an excess of lithium in the presence of a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 10 mol%), a double reductive cleavage takes place to give dianionic intermediate **9**, which by reaction with different electrophiles [H_2O, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$], followed by hydrolysis with water, yields symmetrically 2,2′-disubstituted binaphthyls **7**. In the case of starting from (*R*)-**5a**, the reductive opening by treatment with 2.2 equiv of lithium naphthalenide followed by reaction with H_2O or $(CH_2)_5CO$ as electrophiles and final hydrolysis, leads to enantiomerically pure compounds (*R*)-**6aa** and (*R*)-**6af**, respectively.

Asymmetric synthesis[1] deals with the development of stereodifferentiating reactions in which the source of the information of the stereochemical course can be present in a stoichiometric (chiral auxiliary) or a catalytic (chiral catalyst) amount, the enantioselective catalysis[2] with transition metals in the presence of a chiral ligand being probably one of the most popular research areas in organic chemistry in the last decades. Among chiral ligands, those containing a 1,1′-binaphthyl moiety[3] have played a central role in this field and when substituents are introduced into the 2,2′-positions the atropoisomers become configurationally stable and for that reason easily resolvable.[4] Apart from the interest in the design of binaphthyls for asymmetric synthesis, they can be used in materials science because of the unique properties derived from their rigidity, chirality and conjugation.[5] On the other hand, functionalised organolithium compounds[6] have found a great applicability in organic synthesis because, their reaction with electrophiles yields polyfunctionalised molecules in a single process. These organolithium compounds can be prepared through a wide range of methodologies,[7] the reductive opening of some heterocycles[8] are of special interest due to the accessibility of the starting materials, in many cases in enantiomerically pure form when stereogenic elements are present in their structures. Lithium metal is the lithiating reagent in these electron transfer processes[9] either alone or in the presence of an arene in a stoichiometric or catalytic amount.[10] The reductive opening lithiation takes place only in the case of strained heterocycles (three and four membered-ring heterocycles) and those with activated bonds,[8] for instance, compounds with allylic and benzylic carbon–heteroatom bonds[11] as well as aryl ethers and thioethers. It has been reported that the reductive opening of different 2,7-dihydrodibenzoheteroepines **1**[12,13] by means of excess of lithium in the presence of a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) allows the generation of the corresponding functionalised organolithium intermediates **2**, which can be trapped with different electrophiles to yield compounds **3** (Chart 1). In the case of dihydrodibenzothiepine **1c**, a tandem double sequential lithiation reaction with electrophiles allows the introduction of two equal or different electrophiles at the benzylic positions to give 2,2′-disubstituted biphenyls **4**[13] (Chart 1). With these

Keywords: Reductive ring opening; Dinaphthoheteroepines; DTBB-catalysed lithiation; Electrophilic substitution; Substituted binaphthyls.
* Corresponding author. Tel.: +34 965 909672; fax: +34 965 903549; e-mail: foubelo@ua.es

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.041



1a: Y = O
1b: Y = NMe
1c: Y = S

2a: Y = O
2b: Y = NMe
2c: Y = S

3a: Y = O
3b: Y = NMe
3c: Y = S

4

Chart 1.

antecedents in mind, we considered out of interest to study the reductive opening of different dinaphthoheteroepines **5** in order to prepare unsymmetrical and symmetrical 2,2′-disubstituted-1,1′-binaphthyls **6** and **7**, respectively.

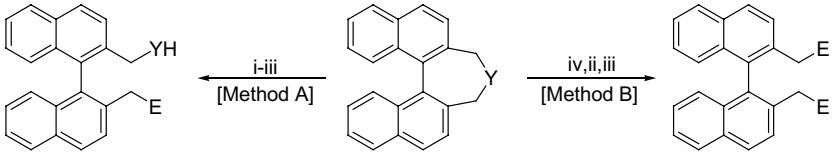
Starting materials **5** were prepared from commercially available 1-bromo-2-methylnaphthalene in only three steps and in around 40% overall yield in both cases. First, aryl–aryl coupling of the mentioned bromoarene with its Grignard reagent in the presence of a catalytic amount of bis[triphenylphosphine]dichloronickel to give 2,2′-dimethyl-1,1′-binaphthyl (**7a**).[14] After that, radical benzylic bromination with *N*-bromosuccinimide in the presence of AIBN[15] gave 2,2′-bis(bromomethyl)-1,1′-binaphthyl. Finally, double nucleophilic substitution by treatment with a 5 M NaOH aqueous solution in dioxane in the presence of 2,6-lutidine[16] and with sodium sulfide nonahydrate[17] afforded compounds **5a** and **5b**, respectively.

The reaction of 2,7-dihydrodinaphthoheteroepines **5** with 2.2 equiv of lithium naphthalenide in THF at −78 °C for 1 h (method A)[18] followed by addition of different electrophiles [H_2O, D_2O, ^tBuCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$] at the same temperature gave, after hydrolysis with water in the case of the oxygen derivative **5a** or a 3 M HCl aqueous solution for the sulfur derivative **5b**, the corresponding hydroxyl or sulfanyl functionalised binaphthyl derivatives **6** in good to moderate yields (Scheme 1, Table 1, entries 1–10). When pivalaldehyde was used as electrophile, a 1:1 mixture of diastereomers was obtained (Table 1, entry 3) and separated by column chromatography.

Regarding the mechanism of this process, it is assumed that the functionalised organolithium compound **8** (Chart 2) is formed after reductive ring opening of the starting heterocycles **5**. In the case of using an excess of lithium metal in the presence of a catalytic amount of DTBB (10 mol%) as the lithiating reagent and after addition of the corresponding electrophile under the same reaction conditions (Method B),[19] it was not possible to obtain the expected functionalised binaphthyls **6** in reasonable yields, even after short reaction times. Instead of that, a significant amount of the symmetrical 2,2′-disubstituted derivatives **7** were obtained as reaction products. The yield of these reactions was improved when 2.2 equiv of the corresponding electrophile [H_2O, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$] were added (Scheme 1, Table 1, entries 11–16). These results indicated that, after the reductive opening of compounds **5** to give dianionic intermediate **8** (Chart 2), a second reductive cleavage of the remaining benzylic carbon–heteroatom bond took place in the highly reductive reaction medium to give the dilithium derivative **9**[20] (Chart 2).

Since both enantiomers of the starting materials **5** can be accessible through already described procedures, this methodology could be applied to the synthesis of 2,2′-disubstituted-1,1′-binaphthyls in an enantiomerically pure form. Thus, heterocycle (*R*)-**5a** was obtained through the methodology described above for the racemic heterocycles, starting from (*R*)-2,2′-dimethyl-1,1′-binaphthyl [prepared from commercially available (*R*)-BINOL (>99% ee) by transforming it into the corresponding bistriflate and performing a bis(triphenylphosphine)dichloronickel-catalysed coupling with methylmagnesium bromide]. Reductive lithiation of (*R*)-**5a** with lithium naphthalenide (Method A) followed by reaction with H_2O and cyclohexanone as electrophiles and final hydrolysis with water gave compounds (*R*)-**6aa**[21a] and (*R*)-**6af**[21b] in 80% and 49% yield, respectively (Scheme 2).

In conclusion, we report here that the reductive opening lithiation of 2,7-dihydrodinaphthoheteroepines **5** at



6

5a: Y = O
5b: Y = S

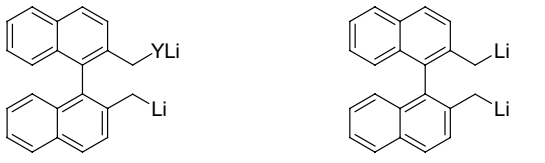
7

Scheme 1. Reagents and conditions: (i) $LiC_{10}H_8$ (2.2 equiv), THF, −78 °C, 1 h; (ii) $E^+ = H_2O$, D_2O, ^tBuCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, −78 °C, 15 min; (iii) H_2O for Y = O or 3 M HCl for Y = S, −78 to 20 °C; (iv) Li, DTBB (10 mol%), THF, −78 °C, 1 h.

Table 1. Preparation of compounds **6** and **7**

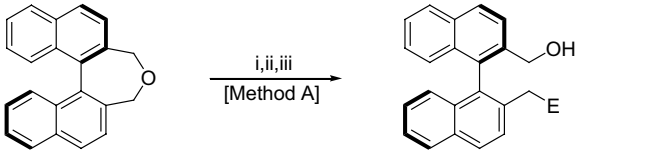
Entry	Starting material	Method	E^+	Product[a]			
				No.	Y	E	Yield[b](%)
1	**5a**	A	H_2O	**6aa**	O	H	81
2	**5a**	A	D_2O	**6ab**	O	D	68[c]
3	**5a**	A	^{t}BuCHO	**6ac**	O	^{t}BuCHOH	48[d]
4	**5a**	A	Me_2CO	**6ad**	O	Me_2COH	38
5	**5a**	A	Et_2CO	**6ae**	O	Et_2COH	51
6	**5a**	A	$(CH_2)_5CO$	**6af**	O	$(CH_2)_5COH$	48
7	**5b**	A	Me_2CO	**6bd**	S	Me_2COH	64
8	**5b**	A	Et_2CO	**6be**	S	Et_2COH	56
9	**5b**	A	$(CH_2)_5CO$	**6bf**	S	$(CH_2)_5COH$	53
10	**5b**	A	$(CH_2)_4CO$	**6bg**	S	$(CH_2)_4COH$	36
11	**5a**	B	H_2O	**7a**	—	H	96
12	**5a**	B	Me_2CO	**7d**	—	Me_2COH	48
13	**5b**	B	Me_2CO	**7d**	—	Me_2COH	52
14	**5b**	B	Et_2CO	**7e**	—	Et_2COH	57
15	**5b**	B	$(CH_2)_5CO$	**7f**	—	$(CH_2)_5COH$	31
16	**5b**	B	$(CH_2)_4CO$	**7g**	—	$(CH_2)_4COH$	38

[a] Products **6** and **7** were ⩾95% pure (GLC and 300 MHz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H, and ^{13}C NMR and LRMS/HRMS).
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **5**.
[c] ~70% Deuterium incorporation (^{13}C NMR).
[d] A ca. 1:1 diastereomeric mixture was obtained and separated by column chromatography (silica gel, hexane/ethyl acetate).



8 **9**

Chart 2.



(*R*)-**5a** (*R*)-**6aa**: E = H (80%)
(*R*)-**6af**: E = $(CH_2)_5COH$ (49%)

Scheme 2. Reagents and conditions: (i) $LiC_{10}H_8$ (2.2 equiv), THF, −78 °C, 1 h; (ii) $E^+ = H_2O$, $(CH_2)_5CO$, −78 °C, 15 min; (iii) H_2O, −78 to 20 °C.

−78 °C with 2.2 equiv of lithium naphthalenide led to dianionic intermediate **8**, which by reaction with electrophiles and final hydrolysis gave unsymmetrical 2,2′-disubstituted-1,1′-binaphthyl derivatives **6**. However, when the lithiation was performed with an excess of lithium metal in the presence of a catalytic amount of DTBB, after reaction with electrophiles and final hydrolysis, the symmetrically substituted binaphthyls **7** were obtained as reaction products, 2,2′-bis(lithiomethyl)-1,1′-binaphthyl (**9**) being the intermediate in this process. This methodology can be applied to the synthesis of enantiomerically pure binaphthyls by using enantiomerically pure dinaphthoheteroepines **5** as starting materials.

Acknowledgements

This work was generously supported by the Dirección General de Enseñanza Superior (DGES) of the current Spanish Ministerio de Ciencia y Tecnología (MCyT; grant no. BQU2001-0538) and the Generalitat Valenciana (projects no. GV01-443 and CTIDIB/2002/318). B.M. thanks the MCyT for a scholarship.

References and notes

1. For monographs, see: *Houben-Weyl Stereoselective Synthesis*; (a) Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1996; (b) *Handbook Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 2003.
2. For monographs, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; (b) *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, 2004.
3. For reviews, see: (a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503–517; (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3211; (c) Kočovský, P.; Vyskočil, S.; Smrčina, M. *Chem. Rev.* **2003**, *103*, 3213–3245.
4. (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 1142; (b) Di Bari, L.; Pescitelli, G.; Salvadori, P. *J. Am. Chem. Soc.* **1999**, *121*, 7998–8004.
5. Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494.
6. For reviews, see: (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155–181; (b) Nájera, C.; Yus, M. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 67–96; (c) Nájera, C.; Yus,

M. *Curr. Org. Chem.* **2003**, *7*, 867–926; (d) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255–9303; (e) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667–2722.

7. For monographs, see: (a) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988; (b) *Lithium Chemistry: A Theoretical and Experimental Overview*; Sapse, A. M., von Ragué Schleyer, P., Eds.; John Wiley & Sons: New York, 1995; (c) Gray, M.; Tinkel, M.; Sniekus, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., McKillop, A., Eds.; Pergamon: Oxford, 1995; Vol. 11, pp 1–92; (d) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002.
8. For reviews, see: (a) Yus, M.; Foubelo, F. *Rev. Heteroat. Chem.* **1997**, *17*, 73–107; (b) Yus, M.; Foubelo, F. *Targets in Heterocyclic Systems* **2002**, *6*, 136–171; (c) Yus, M. *Pure Appl. Chem.* **2003**, *75*, 1453–1475.
9. For mechanistic studies, see: (a) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455–3458; (b) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574–2584; (c) Herrera, R. P.; Guijarro, A.; Yus, M. *Tetrahedron Lett.* **2003**, *44*, 1309–1312; (d) Herrera, R. P.; Guijarro, A.; Yus, M. *Tetrahedron Lett.* **2003**, *44*, 1313–1316.
10. For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155–161; (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–237; (c) Yus, M. *Synlett* **2001**, 1197–1205; (d) Yus, M.; Ramón, D. J. *Latv. J. Chem.* **2002**, 79–92; (e) Ramón, D. J.; Yus, M. *Rev. Cubana Quim.* **2002**, *14*, 75–115; (f) Yus, M. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: Chichester, 2004; Chapter 11.
11. For the last paper on this topic from our laboratory, see: Foubelo, F.; Moreno, B.; Yus, M. *Tetrahedron* **2004**, *60*, 4655–4662.
12. Azzena, U.; Demartis, S.; Pilo, L.; Piras, E. *Tetrahedron* **2000**, *56*, 8375–8382.
13. Foubelo, F.; Yus, M. *Tetrahedron Lett.* **2001**, *42*, 2469–2472.
14. Maigrot, N.; Mazaleyrat, J.-P. *Synthesis* **1985**, 317–320.
15. Bestmann, H. J.; Both, W. *Chem. Ber.* **1974**, *107*, 2926–2930.
16. Kirmse, W.; Kund, K. *J. Org. Chem.* **1990**, *55*, 2325–2332.
17. Stará, I. G.; Starý, I.; Tichý, M.; Závada, J.; Fiedler, P. *J. Org. Chem.* **1994**, *59*, 1326–1332.
18. *Typical procedure for Method A*: To a cooled (−78 °C) solution of compound **5** (0.5 mmol) in THF (2 mL) was added dropwise a 0.7 M THF solution (1.6 mL, 1.1 mmol) of lithium naphthalenide and the mixture was stirred at the same temperature for 1 h. Then the corresponding electrophile was added dropwise (0.6 mmol, 0.25 mL in the case of H_2O and D_2O) and after 15 min it was hydrolysed with water (5 mL) for compound **5a** and with 3 M HCl in the case of **5b**. The resulting mixture was extracted with ethyl acetate (3 × 15 mL) and the organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr). The residue was then purified by column chromatography (silica gel, hexane:ethyl acetate) to yield pure compounds **6**.
19. *Typical procedure for Method B*: To a cooled (−78 °C) blue suspension of lithium powder (105 mg, 15.0 mmol) and a catalytic amount of DTBB (26 mg, 0.1 mmol) in THF (3 mL) was added dropwise a solution of compound **5** (0.5 mmol) in THF (1 mL) under argon and the mixture was stirred at the same temperature for 1 h. Then the corresponding electrophile was added dropwise (0.6 mmol, 0.25 mL in the case of H_2O) and after 15 min it was hydrolysed with water (5 mL). The resulting mixture was extracted with ethyl acetate (3 × 15 mL) and the organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr). The residue was then purified by column chromatography (silica gel, hexane:ethyl acetate) to yield pure compounds **7**.
20. Chong, J. M.; MacDonald, G. K.; Park, S. B.; Wilkinson, S. H. *J. Org. Chem.* **1993**, *58*, 1266–1268.
21. (a) $[\alpha]_D^{20}$ −5.5° (*c* 1.0, $CHCl_3$); 98% ee from HPLC analysis, Daicel Chiralpak AS, λ = 254 nm, *n*-hexane/2-propanol, 1.0 mL/min, t_r = 7.73 and 10.00 min. (b) $[\alpha]_D^{20}$ +70° (*c* 0.8, CH_2Cl_2); 98% ee from HPLC analysis, Daicel Chiralpak AS, λ = 254 nm, *n*-hexane/2-propanol, 1.0 mL/min, t_r = 25.70 and 29.69 min.