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A new approach toward the synthesis of heterolignans

Frédéric Garzino, Alain Méou and Pierre Brun*

Laboratoire de Synthèse Organique Sélective, GCOM2, UMR-CNRS 6114, Université de la Méditerranée, case 901, 163 Avenue de Luminy, 13288, Marseille Cedex 9, France

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Abstract—The $SnCl_4$-mediated rearrangement of 2,5-disubstituted-2,3-dihydrofurans in which one of the substituents is a heterocycle was developed as a key step for the synthesis of diverse heterolignans.

Considerable work has been devoted to the synthesis of lignans and their derivatives due to their wide-ranging pharmacological properties.[1–3] More recently, heterolignans have also been reviewed and promising antineoplastic agents were discovered in this class of compounds.[4,5] A heterolignan substructure can also be found in pharmacologically promising new molecules such as potent dopamine D1 agonists used for the treatment of Parkinson's disease.[6] As a consequence, new methods were developed for their synthesis.[7]

Looking for an easy and versatile entry to the synthesis of such compounds we envisioned, as the key step, the $SnCl_4$-rearrangement of 2,5-disubstitued-2,3-dihydrofurans in which one of the substituents would be a heterocycle. Such an approach, initially reported by Fristad from 2,5-diaryl-2,3-dihydrofurans,[8] allows the direct formation of various 4-aryltetralones in high yield provided that both substituents are electron rich aromatic nuclei (Scheme 1),[9] and has recently been utilized in our group in the total synthesis of the enantiopure aryltetralin lignan (+)-phyltetralin.[10]

We thought that, if this rearrangement could be extended to 2,3-dihydrofurans bearing a 2- or a 5-heteroaryl substituent, it would provide a straightforward access to 4-heteroaryltetralones or 4-arylpseudotetralones. Obviously, for this approach to be synthetically useful, we had first to demonstrate that the requisite 2,5-aryl/heteroaryl-2,3-dihydrofurans could be prepared, like their diaryl counterparts, by $Mn(OAc)_3$-mediated oxidative addition involving cinnamate-like esters **3** and benzoyl-like β-keto esters **2** (Scheme 2). Accordingly, we describe herein our preliminary results regarding these two successive steps.[11]

The starting materials **2** and **3** could be easily prepared in good yields: β-keto esters **2** were synthesized according to the method described by Wemple[12] while olefins **3** were obtained by a Doebner condensation performed on the appropriate aromatic or heteroaromatic aldehyde.[13]

As displayed in Table 1, the addition (step 1) failed in four cases (entries 3, 6, 8, 10). In the seven others, it was totally regio- and diastereoselective, giving rise to the single *trans* diastereomer **1** in low (15–19%, entries 2 and 5) to moderate (40–56%, entries 1, 4, 7, 9, 11) yields using as yet unoptimized reaction conditions. Overall, the best results were obtained when the 2- or 3-thienyl moiety was incorporated into either **2** or **3** (entries 1, 7, 9). The other heteroaryls tested allowed to obtain **1** only when incorporated into **2** (entries 2, 4).

Concerning the Lewis acid-rearrangement (step 2), except when it totally failed (entries 4, 5), the conversion of **1** furnished **4** in high yields when conducted in CH_2Cl_2 at room temperature (70–95%, entries 1, 2, 7, 11) or in refluxing $CHCl_3$ (80%, entry 9).

It must be noted that the ^1H NMR spectra of 2-carbalkoxy-4-aryltetralones display a complex pattern denoting the establishment of a tautomeric equilibrium in which the enol form is largely predominant.[10,14] Interestingly, when $Ar^1 = 2$- or 3-thienyl (entries 7, 9, 11) only the enol form (**4ba**, **4da**, **4ga**) can be detected in the ^1H NMR spectrum in $CDCl_3$ (Scheme 3). Conversely, no tautomeric equilibrium exists for the two 4-arylpseudotetralones **4ab** and **4ac** (entries 1 and 2): in

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* Corresponding author. Tel.: 33(0)491829270; fax: 33(0)491829415; e-mail: brun@chimlum.univ-mrs.fr

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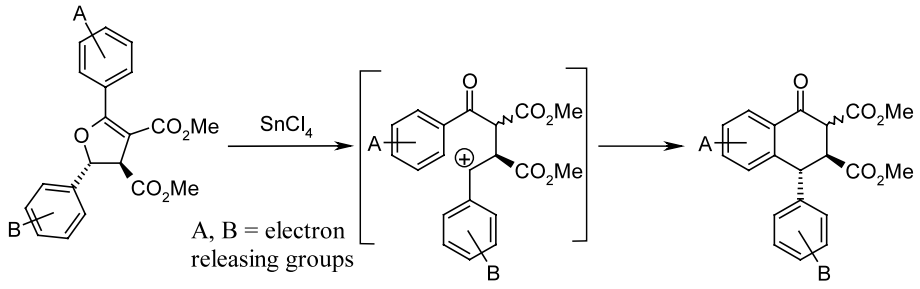
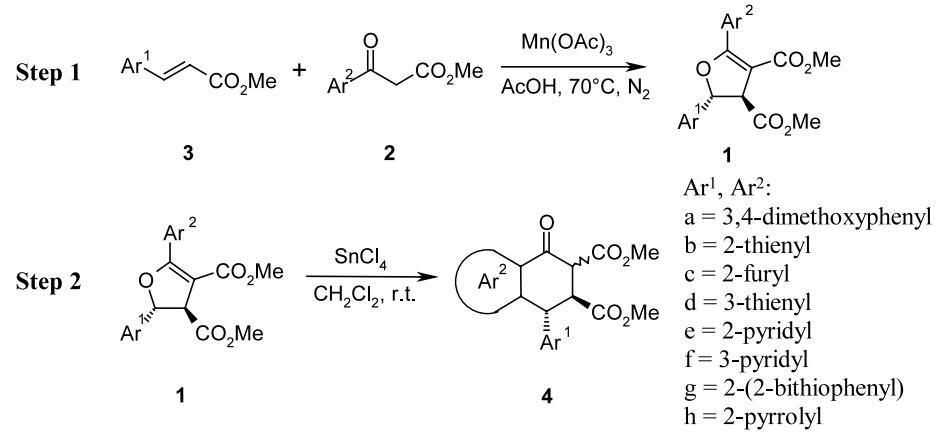


Scheme 1.



Scheme 2.

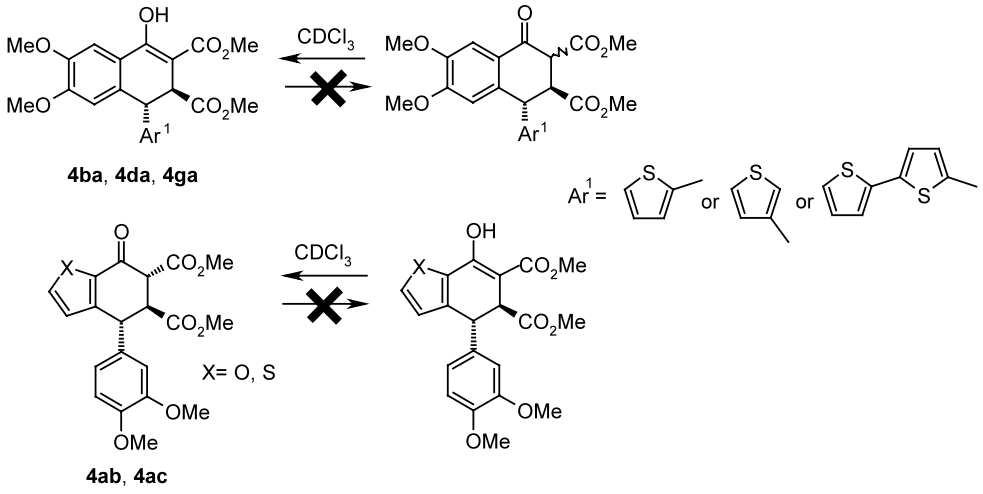
Table 1. Formation of **1** (step 1) and its subsequent rearrangement (step 2)

			Step 1			Step 2		
Entry	Ar^1	Ar^2	Time (h)	Yield **1** (%)[a]	Unreacted **3** (%)	Time (h)	Yield **4** (%)[a]	Unreacted **1** (%)
1	a	b	2	56	28	12	90	0
2	a	c	0.75	19	60	12	70	0
3	a	e	0.25	–	100	–	–	–
4	a	f	4	40	40	48[b]	0	100
5	a	g	2.5	15	60	12	0	0
6	a	h	0.25	–	100	–	–	–
7	b	a	2.5	58	26	2	95	0
8	c	a	0.25	–	100	–	–	–
9	d	a	2	55	20	48[b]	80[c]	5
10	e	a	0.25	–	100	–	–	–
11	g	a	1	43	35	24	87	0

[a] Pure isolated products (unoptimized yields).
[b] The reaction was carried out in refluxing $CHCl_3$.
[c] Accompanied by the corresponding α-decarbomethoxylated tetralone (5%).

each case, the ^1H NMR spectrum ($CDCl_3$) exhibits only the signals corresponding to the all *trans* β-keto ester form.

In summary, we have shown that some 4-heteroaryltetralones and 4-arylpseudotetralones can be prepared (with total control of the relative configuration of two or three contiguous stereogenic centers) in two steps from readily available starting materials. Following experimental optimization (which we are currently investigating), this approach could thus constitute a valuable alternative for the short synthesis of nonnatural aryltetralin lignans.



Scheme 3.

References

1. (a) Ward, R. S. *Chem. Soc. Rev.* **1982**, 75–125; (b) Ward, R. S. *Tetrahedron* **1990**, *46*, 5029–5041; (c) Ward, R. S. *Synthesis* **1992**, 719–730.
2. Damayanthi, Y.; Lown, W. *Curr. Med. Chem.* **1998**, *5*, 205–252.
3. (a) Rao, C. B. S. *Chemistry of Lignans*; Andhra University Press: Waltair, 1978; (b) Ayres, D. C.; Loike, J. D. *Lignans: Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, 1990.
4. Ramos, A. C.; Peláez-Lamamié de Clairac, R.; Medarde, M. *Heterocycles* **1999**, *51*, 1443–1470.
5. (a) Leteurtre, F.; Madalengoitia, J.; Orr, A.; Guzi, T.; Lehnert, E.; Macdonald, T.; Pommier, Y. *Cancer Res.* **1992**, *52*, 4478–4483; (b) Tepe, J. J.; Madalengoitia, J. S.; Slunt, K. M.; Werbovetz, K. A.; Grant Spoors, P.; Macdonald, T. L. *J. Med. Chem.* **1996**, *39*, 2188–2196; (c) Madalengoitia, J. S.; Tepe, J. J.; Werbovetz, K. A.; Lehnert, E. K.; Macdonald, T. L. *Bioorg. Med. Chem.* **1997**, *5*, 1807–1815.
6. (a) Rascol, O.; Blin, O.; Thalamas, C.; Descombes, S.; Soubrouillard, C.; Azulay, P.; Fabre, N.; Viallet, F.; Lafnitzegger, K.; Wright, S.; Carter, J. H.; Nutt, J. G. *Ann. Neurol.* **1999**, *45*, 736–741; (b) Ehrlich, P. P.; Ralston, J. W.; Michaelides, M. R. *J. Org. Chem.* **1997**, *62*, 2782–2785.
7. Ramos, A. C.; Peláez, R.; López, J. L.; Caballero, E.; Medarde, M.; San Feliciano, A. *Tetrahedron* **2001**, *57*, 3963–3977.
8. Yang, F. Z.; Trost, M. K.; Fristad, W. E. *Tetrahedron Lett.* **1987**, *28*, 1493–1496.
9. In the same conditions, 2,5-diaryl-2,3-dihydrofurans possessing electron withdrawing groups on the aromatic nuclei were recovered unchanged. Nevertheless, treatment with Brönsted acids (*p*-TsOH in refluxing toluene, CF_3CO_2H) led to α-benzoyl-γ-butyrolactones in moderate yields (35%).
10. Garzino, F. Ph.D. Thesis, Université de la Méditerranée, 2001.
11. General procedure for the preparation of 2,3-dihydrofurans **1** and their rearrangement: Olefin **3** (1 mmol), β-keto ester **2** (1 mmol) and $Mn(OAc)_3{\cdot}2H_2O$ (590 mg, 2.2 mmol) in acetic acid (10 mL) were heated at 70°C under nitrogen until complete discoloration. After cooling, H_2O was added and the mixture extracted with Et_2O. The organic extracts were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent afforded the crude product which was purified by flash chromatography (hexane/Et_2O: from 16:1 to 1:1). Compound **1** (0.04 M solution in CH_2Cl_2) was stirred under nitrogen at room temperature. 10 equiv. of $SnCl_4$ were added in one portion via a syringe and stirring was continued until total consumption of starting material. The reaction mixture was then diluted with Et_2O followed by careful addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash chromatography (hexane/EtOAc or hexane/Et_2O).
12. Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290–292.
13. Koo, J.; Fish, M. S.; Walker, G. N.; Blake, J. *Organic Syntheses* (Coll. Vol. IV); Wiley: New York, 1963; pp. 327–329.
14. Peterson, J. R.; Winter, T. J.; Do, H. D.; Rogers, R. D. *J. Crystallogr. Spectrosc. Res.* **1989**, *19*, 135–145.