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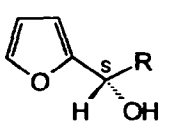
A New Synthetic Route to Optically Active α-Alkyl- 2- and 3-Furylcarbinols by Intramolecular Diastereoselectivity

LAURENT D. GIRODIER and FRANCIS P. ROUESSAC

Laboratoire de Synthèse Organique – URA 482 du CNRS
Faculté des Sciences, Avenue O. Messiaen, Université du Maine, 72017 Le Mans Cedex, France

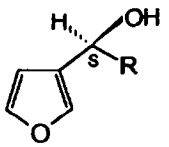
Abstract : *We report the results of intramolecular asymmetric alkylation of enantiomerically pure 2- and 3-furaldehydes containing a p-tolylsulfoxide group, thus providing an efficient method of obtaining optically active α-alkyl-2- and 3-furanmethanol of known configuration after cleavage of the sulfoxide group. In example, R and S α-phenyl-3-furanmethanol are described.*

Optically active 2- and 3-furyl alcohols are versatile materials met in the synthesis of a variety of biologically active compounds and natural products[1], because the furyl group is recognized as important for the facile introduction of further functionalities[2]. Therefore several methods have been used to synthesize these alcohols[3]. Among them, the preparation of optically active (R)- and (S)-α−alkyl furylcarbinols of type **1** by kinetic resolution of racemic furyl alcohols by Sharpless asymmetric oxidation[4], or enantioselective alkylation of furaldehydes using a kinetically formed chiral complex between Grignard-zinc halide reagents and an optically pure β−amino alcohol have been used[5]. In contrast the asymmetric synthesis of 3-furyl alcohols of type **2** has been explored to a much lesser extent[6].



type **1**

R = alkyl group

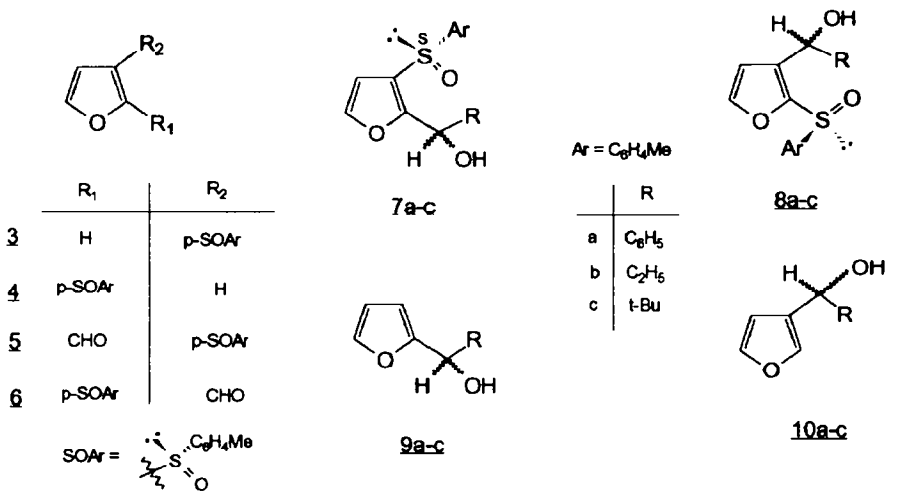


type **2**

We report here that chiral furyl p-tolylsulfoxides **3** and **4**, described in a previous paper[7], may be used as an alternative for the preparation of these alcohols. The results obtained with R = Ph allowed for instance to ascertain the absolute configurations of **(S)-10a** and **(R)-10a** of type 2, unknown until now in optically active form.

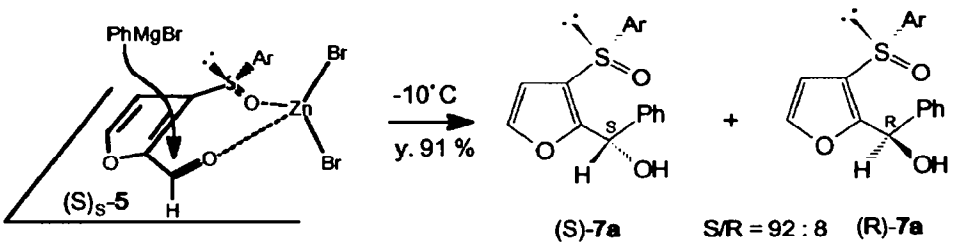
In the early stage, we tried to get pure enantiomers of type **1** alcohols through 1,2-addition of aldehydes RCHO (R=Ph, Et, tBu) to 2-furyllithium derivative **3**. However, in each case, the desired alcohols were produced in very low enantiomeric excesses (20-30 %) under a variety of reaction conditions (Table 1, entries 1-5). Only small amounts of the pure target molecules were obtained after laborious purification by column chromatography on silica gel. It is also to be noted that when **4** was treated by BuLi in order to form the carbanion, this intermediate underwent 1,2 C-C sulfoxide group migration on furan ring, leading to the more

stable isomer 3 and alcohol 7 as racemates. This is not without similarity to the TMS group migration recently described[8]. This failure led us to explore an alternative which involved the reaction of organometallic compounds upon the aldehydes 5 and 6[9] (scheme 1) in the presence of variable proportions of Lewis acids.



Scheme 1

As can be seen from Table 1 (entries 6-23), temperature, alkylmetal and Lewis acid modify the d.e. of each run. If no Lewis acid was present, the organometallic gave rise to a mixture for which *R*-alcohol was predominant (entries 8, 9, 14, 15). If ZnX_2 was added before the organometallic compound (entries 6, 7, 10-13), stereoselection could be inversed if temperature was raised (runs 11-13 *versus* 10). Attack at the less hindered face of a chelated[10a] bromomagnesium or organozincate[10b] intermediate (scheme 2) rationalises the complementary diastereoselection obtained upon direct reaction with organometallics. Due to the racemization of 6 in the presence of Grignard reagent, transmetallation with titanium isopropoxide was chosen. It was noticed that conformationally rigid phenyl group gave the highest enantioface differentiation of carbonyl plane of 5. So, with PhMgBr, a $S,S_{(S)}$ diastereomeric excess of 84% was obtained (entry 13 and scheme 2).



Scheme 2

Diastereomeric mixtures of sulfoxide alcohols 7 or 8 could be separated by low pressure liquid chromatography except for 7a and 8a (R=Ph) which were firstly transformed into their acetates, then after hydrolysis, into optically active carbinols 9a and 10a.

Table 1. Formation of sulfoxide alcohols 7 and 8 from sulfoxides 3 to 6.

entry	substrate	base	Lewis a. (eq)	reagent	temp.°C	time (h)	conv (%)[a]	alcohol[b]	y. (%)[c]	RS_s/SS_s[d]
1	3	n-BuLi		PhCHO	-78	2	40	7a(R)/7a(S)	30	39/61
2	3	LDA		PhCHO	-78	2	93	7a(R)/7a(S)	73	36/64
3	3	LDA		EtCHO	-78	1,5	66	7b(R)/7b(S)	61	43/57
4	3	n-BuLi		t-BuCHO	-78	3	100	7c(R)/7c(S)	57	47/53
5	3	LDA		t-BuCHO	-78	1	84	7c(R)/7c(S)	67	44/56
6	5		$ZnBr_2$(3)	t-BuMgCl	-15	1	66	7c(R)/7c(S)	47	60/40
7	5		$ZnCl_2$(5)	EtMgBr	0	2	76	7b(R)/7b(S)	62	35/65
8	5			PhMgBr	RT	2	88	7a(R)/7a(S)	75	62/38
9	5			PhMgBr	-78[e]	5	95	7a(R)/7a(S)	82	73/27
10	5		$ZnCl_2$(3)	PhMgBr	-78[e]	3	91	7a(R)/7a(S)	85	61/39
11	5		$ZnCl_2$(3)	PhMgBr	-5	2	92	7a(R)/7a(S)	90	17/83
12	5		ZnI_2(3)	PhMgBr	-10	2	64	7a(R)/7a(S)	57	15/85
13	5		$ZnBr_2$(3)	PhMgBr	-10	2	93	7a(R)/7a(S)	91	8/92
14	5			$PhTi(OiPr)_3$	-5	1	95	7a(R)/7a(S)	93	67/33
15	5			$PhTi(OiPr)_3$	-78	2	92	7a(R)/7a(S)	90	76/26
16	6			PhMgBr	-5	0,75		8a(R)/8a(S)	*	
17	6		$ZnBr_2$(3)	PhMgBr	-10	2	86	8a(R)/8a(S)	85	15/85[f]
18	6		$ZnBr_2$(3)	$PhTi(OiPr)_3$[h]	-5	2	46	8a(R)/8a(S)	33	61/39[g]
19	6			$PhTi(OiPr)_3$[i]	10	2	91	8a(R)/8a(S)	58	76/24[g]
20	6			$PhTi(OiPr)_3$[j]	-5/-78[e]	2	88	8a(R)/8a(S)	73	74/26[g]
21	6			$PhTi(OiPr)_3$[k]	-78[e]	2	66	8a(R)/8a(S)	22	75/25
22	6			$PhTi(OiPr)_3$[l]	-78[e]	2	87	8a(R)/8a(S)	83	40/60
23	6			$PhTi(OiPr)_3$[m]	-55[e]	2	100	8a(R)/8a(S)	97	46/54

a) Conversion ratio determined by ^1H NMR. The presence of by-products explains the difference between yield and conversion ratio.
b) By preparative liquid chromatography, we noticed that the first eluted diastereomer had the *SS* configuration. The assignement *R* or *S* to the C center was made possible by comparaison of signs of optical rotations after cleavage to known alcohols. See stereochemistry abstracts at the end of this issue for the description of some of them.
c) Alcohols were separated from the reaction mixture with flash column chromatography. Product ratio were determined by repeated integrations of proton signals.
d) % d.e. RS_s/SS_s determined by ^1H NMR with [Eu(hfc)$_3$] shift reagent (mixture test was positive).
e) The reaction mixture was warmed up to RT before treatement.
f) Two diastereomers isolated as racemates.
g) some racemization occured.
h) 1,8 eq. Grignard reagent + 0,9 eq $TiCl(O\text{-}iPr)_3$
i) 1.3 eq. Grignard reagent + 0.35 eq $TiCl(O\text{-}iPr)_3$
j) 2 eq. Grignard reagent + 1 eq $TiCl(O\text{-}iPr)_3$
k) 1 eq. Grignard reagent + 2 eq $TiCl(O\text{-}iPr)_3$
l) 1.4 eq. Grignard reagent + 1.4 eq $TiCl(O\text{-}iPr)_3$
m) 2 eq. Grignard reagent + 2 eq $TiCl(O\text{-}iprOiPr)_3$
* PhMgBr gave cleavage of the SOAr group Racemic alcohol was isolated.

Sulfoxide cleavage was performed without loss of enantiomeric excess, upon treatment with t-BuLi. The mechanism probably consists in a rapid ligand exchange reaction leading to the C–S bond cleavage at low temperature[11].

The absolute configurations of alcohols **2** were determined by chemical correlation to (S)-2-alkylfurylcarbinols already known[12]. The absolute configuration of one of the two diastereoisomers **8a** was established as *(S,S)* by X-ray diffraction[13]. By cleavage of the sulfoxide group as above mentioned, this diastereoisomer gave **(S)-10a**.

In summary the methodology described above provides a new entry to enantiomerically pure furylcarbinols by using simple conditions. Further studies on the application of our process are now being pursued to improve the asymmetric induction.

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