Regioselective Synthesis of Trisubstituted Cyclopentadienyl Ligands from Furans

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Received 29 May 2002

Abstract: 1,2,3- And 1,2,4-trisubstituted cyclopentadienyl manganese tricarbonyl compounds have been synthesized regioselectively from furans following a common synthetic strategy. The key steps include the transformation of furylcarbinols into hydroxycyclopentenones followed by the conjugate addition of Grignard reagents under chelation directed conditions. This affords hydroxycyclopentanones which can be dehydrated to cyclopentenones. These compounds are further elaborated into the final targets by the 1,2-addition of organolithium reagents.

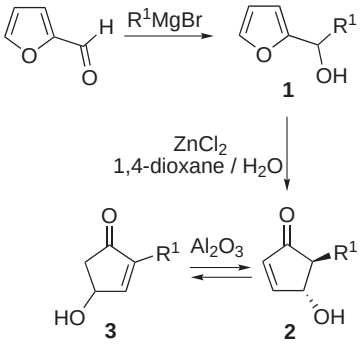
Key words: cyclopentadienes, furans, metallocenes, manganese, organometallic reagents

Cyclopentadienyls constitute one of the most important types of ligands in organometallic chemistry.[1] It is well known that the substitution pattern of the cyclopentadienyl moiety can significantly modify the properties of metallocenes.[2] Therefore, the development of new efficient approaches for the easy generation of polysubstituted cyclopentadienyls in a regioselective fashion is of continuing importance.[3]

Trisubstituted cyclopentadienyl ligands can be conveniently prepared either by the deprotonation of the corresponding cyclopentadienes or by the addition of hydride or carbon nucleophiles to fulvenes.[3] Both approaches require the functionalization of simpler disubstituted cyclopentadienes, which are used as starting materials. However, in most cases the deprotonation of disubstituted cyclopentadienes followed by reaction with alkyl halides or carbonyl compounds suffers from poor regioselectivity, giving rise to mixtures of isomeric trisubstituted cyclopentadienes or fulvenes. Also, the alkylation of disubstituted cyclopentadienes cannot be used for the introduction of aryl groups on the cyclopentadienyl moiety. Therefore, alternative synthetic strategies must be devised. The functionalization of cyclopentenones appears particularly attractive in this context, and different procedures have been reported for the synthesis of this kind of compounds.[4] However, most of these methods either do not allow for the introduction of three different aryl groups, or are limited to only one type of substitution pattern (1,2,3- or 1,2,4) in the final cyclopentadiene.[5]

Among the different procedures for the assembly of cyclopentenones, we were particularly interested in the use of simple furan derivatives as starting material. This method is characterized by the ready availability of the precursors and the simplicity of the synthetic procedures,[6] which may be of interest from a large-scale synthesis standpoint. We report herein the regioselective preparation of 1,2,3- and 1,2,4-trisubstituted cyclopentadienes by means of a common synthetic strategy starting from furfural and simple Grignard and organolithium reagents.

Furylcarbinols **1** can be prepared by a variety of procedures.[7] Among these methods, the nucleophilic addition of organolithiums or Grignard compounds (R^1M) to inexpensive furfural is particularly attractive. Compounds **1** can be rearranged to the 4-hydroxycyclopentenones **2** by acid treatment, and the latter can be isomerized to the 4-hydroxycyclopentenones **3** (Scheme 1). This first step allows for the introduction of the first substituent (R^1) of the final cyclopentadienyl.

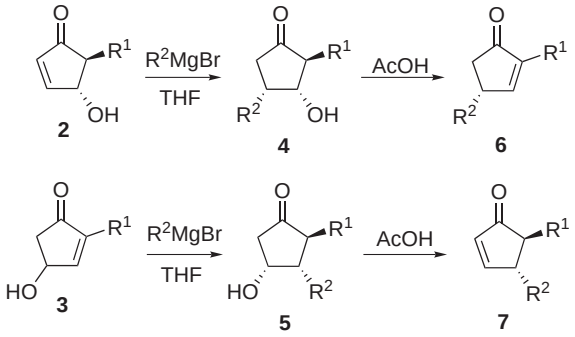


Scheme 1

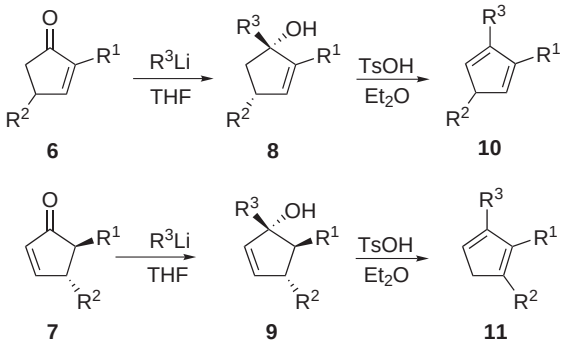
The introduction of the second substituent (R^2) has been accomplished by addition of Grignard reagents to hydroxycyclopentenones **2** or **3** (Scheme 2). The reaction takes place regioselectively in a 1,4-fashion when carried out in THF solution, with no need of the presence of Cu(I) salts or co-solvents.[8] This step is crucial in determining the regiochemistry of the final trisubstituted cyclopentadienyl ligand: when the reaction was carried out starting from 4-hydroxycyclopentenones **2**, substituents R^1 and R^2 ended up in a 1,3-relative disposition giving rise to compounds **4**; while starting from compounds **3**, allowed for a 1,2-relative disposition between R^1 and R^2 affording compounds **5**.[9]

Synlett 2002, No. 9, Print: 02 09 2002.
Art Id.1437-2096,E;2002,0,09,1451,1454,ftx,en;G14902ST.pdf.

ISSN 0936-5214



Scheme 2



Scheme 3

However, partial dehydration of compounds **4** to **6** was observed either upon standing in $CHCl_3$ solution or under silica gel chromatography conditions.[10] This spontaneous dehydration was not observed for the regioisomeric compounds **5**. Both types of hydroxycyclopentanones could be quantitatively dehydrated to cyclopentenones **6** and **7** in HOAc solution. Therefore, the synthesis of compounds **6** and **7** could be conveniently carried out in a one pot procedure starting from hydroxycyclopentenones **2** and **3** without isolation of the intermediate hydroxycyclopentanones **4** and **5**. The results of the overall transformation of compounds **2** and **3** to cyclopentenones **6** and **7** are given in Table 1.[11]

Table 1 Synthesis of Compounds **6** and **7** from Furylcarbinols **1**

No.	**1**	**2**	R^1	R^2	**6**, **7** (%)[a]
1	**1b**	**2b**	Ph	Ph	**6a** (55)
2	**1b**	**2b**	Ph	Me	**6b** (55)
3	**1b**	**2b**	Ph	*p*-MeO-Ph	**6c** (60)
4	**1b**	**2b**	Ph	p-CF_3-Ph	**6d** (60)
5	**1a**	**3a**	Me	Ph	**7a** (75)
6	**1b**	**3b**	Ph	Me	**7b** (65)
7	**1b**	**3b**	Ph	Ph	**7c** (70)
8	**1b**	**3b**	Ph	*p*-MeO-Ph	**7d** (70)
9	**1b**	**3b**	Ph	*p*-CF_3-Ph	**7e** (75)

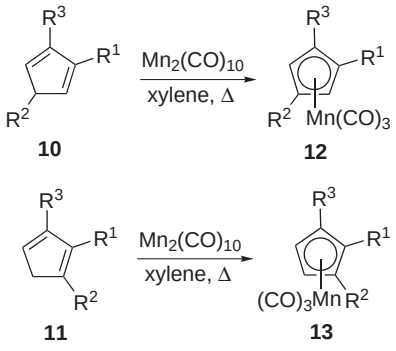
[a] Isolated yields.

The introduction of the third substituent (R^3) of the final trisubstituted cyclopentadienyl ligand was carried out by the 1,2-nucleophilic addition of organolithium or Grignard reagents to the carbonyl group of compounds **6** and **7** (Scheme 3). Dehydration of the intermediate vinylcarbinols **8** and **9** with catalytic amounts of TsOH in Et_2O solution gave rise to cyclopentadienes **10** and **11**.[12] The results of the synthesis of compounds **8**–**11** are gathered in Table 2.[13,14]

The addition of organolithiums to the carbonyl group of compounds **6** took place with high diastereoselectivity in favor of the products **8** with 1,4-*cis* stereochemistry.[8] Only in those cases where R^2 was alkyl (**6b**, Table 2, entries 3 and 4) minor amounts of the 1,4-*trans* isomers were detected in the ^1H NMR spectra of the crude reaction products. These could be separated by chromatography.

Similarly, the addition of R^3M to the carbonyl group of cyclopentenones **7** led to major formation of the corresponding compounds **9** with 1,5-*cis*-4,5-*trans* stereochemistry in those cases where R^3 was aryl.[15] However, the reaction was found to be sensitive to the nature of R^3, as the addition of MeLi to **7c** (Table 2, entry 13) led to compound **9d** as a 1:1 mixture of 1,5-*cis*-4,5-*trans* and 1,5-*trans*-4,5-*trans* isomers. Dehydration of hydroxycyclopentenes **8** and **9** with calalytic amounts of TsOH in Et_2O solution gave rise to cyclopentadienes **11** and **12** (Scheme 3).

The use of these compounds as ligands in organometallic chemistry has been tested in the case of the synthesis of the cyclopentadienylmanganesetricarbonyl compounds **12** and **13**. In this way, metalation of **10** and **11** was carried out (Scheme 4) by treatment with $Mn_2(CO)_{10}$ in refluxing xylene for 24 h, giving rise to the corresponding trisubstituted cyclopentadienyl mangansese compounds **12** and **13**.[16] The scope of the transformation of furylcarbinols **1** into the trisubstituted cyclopentadienyl manganese tricarbonyls **13** and **14** is given in Table 2.[17]



Scheme 4

Table 2 Synthesis of Trisubstituted Cyclopentadienyls

No	**6**, **7**	R^1	R^2	R^3	**8**, **9** (%)[a]	**10**, **11** (%)[a]	**12**, **13** (%)[a]
1	**6a**	Ph	Ph	Ph	**8a** (70)	**10a** (95)	**12a** (85)
2	**6a**	Ph	Ph	Me	**8b** (80)	**10b** (95)	**12b** (80)
3	**6b**	Ph	Me	Ph	**8c** (80)	**10c** (90)	**12c** (85)
4	**6b**	Ph	Me	Me	**8d** (70)	**10d** (90)	**12d** (80)
5	**6c**	Ph	*p*-MeO-Ph	*p*-MeO-Ph	**8e** (65)	**10e** (80)	**12e** (85)
6	**6c**	Ph	*p*-MeO-Ph	*p*-CF_3-Ph	**8f** (65)	**10f** (80)	**12f** (80)
7	**6d**	Ph	*p*-CF_3-Ph	*p*-MeO-Ph	**8g** (55**)**	**10g** (80)	**12g** (80)
8	**6d**	Ph	*p*-CF_3-Ph	*p*-CF_3-Ph	**8h** (65)	**10h** (80)	**12h** (75)
9	**7a**	Me	Ph	Ph	**9a** (90)	**11a** (50)	**13a** (75)
10	**7b**	Ph	Me	Ph	**9b** (90)	**11b** (80)	**13b** (90)
11	**7c**	Ph	Ph	Ph	**9c** (85)	**11c** (95)	**13c** (85)
12	**7c**	Ph	Ph	Me	**9d** (70)	**11a** (90)	**13a** (75)
13	**7d**	Ph	*p*-MeO-Ph	*p*-MeO-Ph	**9e** (90)	**11d** (75)	**13d** (60)
14	**7d**	Ph	*p*-MeO-Ph	*p*-CF_3-Ph	**9f** (85)	**11e** (70)	**13e** (55)
15	**7e**	Ph	*p*-CF_3-Ph	*p*-CF_3-Ph	**9g** (50)	**11f** (65)	**13f** (50)

[a] Isolated yields.

In summary, we have developed a procedure, which allows for regioselective synthesis of 1,2,3- and 1,2,4-cyclopentadienyl manganese compounds starting from the same precursors and making use of a common synthetic strategy. This method allows the introduction of different alkyl or aryl groups at will on a trisubstituted cyclopentanyl ring in a completely regioselective fashion.

Acknowledgement

Ministerio de Ciencia y Tecnología (Project BQU2000-0653) and REPSOL-YPF are gratefully thanked for financial support.

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(7) General methods for the preparation of furylcarbinols include the reduction of furfuryl ketones, which in turn are obtained from the Friedel–Crafts reaction on furans, or by the reaction of metallated furans with electrophiles. See: Sargent, M. V.; Dean, F. M. In *Comprehensive Heterocyclic Chemistry*, Vol. 4; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, **1984**, Chap. 3.11.
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(9) The addition of the organomagnesium reagent to the hydroxycyclopentenones **3** took place in a completely diastereoselective fashion giving rise to a 2,3-*trans*-3,4-*cis* stereochemistry for compounds **4**. See ref. 8.
(10) All compounds described throughout this work are racemic.
(11) General procedure for the synthesis of cyclopentenones **6** and **7**: To a solution of the corresponding hydroxycyclopentenone **2** or **3** (5 mmol) in THF (25 mL) at 0 ºC was dropwise added a solution of ArMgX (11.0 mmol, 1 M solution in THF) or MeMgI (11.0 mmol, 3 M solution in Et_2O). The mixture was heated at reflux for 2 h, cooled to r.t., and hydrolyzed with saturated NH_4Cl solution (10 mL). After extraction with EtOAc (3 × 25 mL) the combined extracts were dried on $MgSO_4$ and the solvent was evaporated under reduced pressure. The resulting oil was dissolved in HOAc (20 mL) and the solution was heated at reflux for 2 h. The mixture was cooled to r.t. and the solvent was evaporated under reduced pressure. The remaining oil was taken in Et_2O (20 mL) and washed with saturated $NaHCO_3$ (2 × 10 mL) and brine (1 × 15 mL). The solution was dried on $MgSO_4$ and the solvent evaporated under reduced pressure to afford an oil which was purified by chromatography (hexane–EtOAc, 8:1).
(12) Compounds **10** and **11** were obtained as mixtures of double bond isomers.

(13) General procedure for the synthesis of cyclopentenols **8** and **9**: To a solution of cyclopentenone **6** or **7** (1 mmol) in THF (10 mL) at –78 ºC was dropwise added a solution of R^3Li (1.6 mmol, 1.6 M solution of MeLi in THF, 1.8 M solution of PhLi in cyclohexane–Et_2O, or 1.0 M solution of ArLi in THF). The temperature was slowly raised to r.t. and was further stirred for 18 h. The mixture was hydrolyzed with saturated NH_4Cl (10 mL) and extracted with Et_2O (3 × 15 mL). The combined extracts were dried on $MgSO_4$ and the solvent was eliminated under reduced pressure to afford an oil which was purified by silica gel chromatography (hexane–EtOAc, 8:1).

(14) General procedure for the synthesis of cyclopentadienes **10** and **11**: To a solution of **8** or **9** (3 mmol) in Et_2O (6 mL) was added TsOH (0.6 mmol) and the solution was stirred at r.t. until disappearance of the starting material by TLC (1–6 h). The mixture was diluted with Et_2O (20 mL) and washed with saturated $NaHCO_3$ (2 × 10 mL) and brine (1 × 15 mL). The organic layer was dried on $MgSO_4$ and the solvent was eliminated under reduced pressure. The resulting oil was purified by chromatography (hexane–Et_2O, 40:1).

(15) The stereochemistry of **9d** was determined by NOE experiments.

(16) No dealkylation of the methyl-substituted cyclopentadienes was observed under these reaction conditions. See ref. 5.

(17) General procedure for the synthesis of **12** and **13**: A solution of **10** or **11** (1.8 mmol) and $Mn_2(CO)_{10}$ (2.0 mmol) in xylene (80 mL) was heated at reflux for 24 h. The solvent was eliminated under reduced pressure and the crude reaction product was purified by chromatography (hexane–Et_2O, 10:1).