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A New Simple Route to Furanic Ketones; Preparation of Elsholtzione, Naginata Ketone and Perilla Ketone[1].

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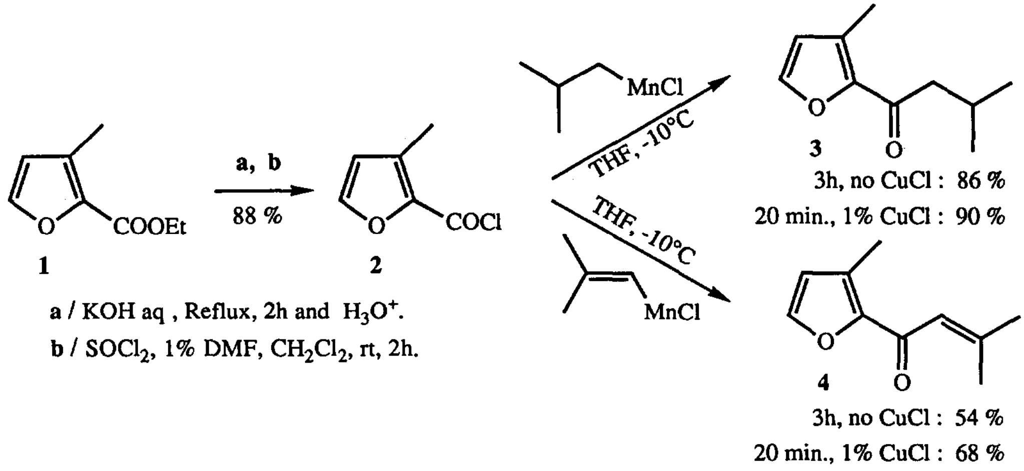
Abstract: *Copper- or iron-catalyzed acylation of organomanganese reagents allows to obtain 3- and 2-acylfurans in high yields. Elsholtzione, naginata ketone and perilla ketone have been prepared according to this procedure.*

Recently, we have shown that a vast array of ketones can be easily prepared in high yields by acylation of organomanganese reagents[2]. Now, we report an application of this method to the synthesis of three natural furanic ketones[3]: elsholtzione **3**[4], naginata ketone **4**[5] and perilla ketone **6**[6].

Elsholtzione **3** and naginata ketone **4** were prepared according to Scheme I. The synthesis of the starting ethyl 3-methyl-2-furoate **1** has already been described[7]. Saponification of **1**, then treatment of the crude carboxylic acid thus obtained with thionyl chloride, afforded 3-methylfuroyl chloride **2**. Acylation, under mild conditions, of isobutyl manganese chloride and 2-methyl propenyl manganese chloride by the carboxylic acid chloride **2** gave the ketones **3** and **4** in excellent yields[8]. In both cases, the addition of cuprous chloride as catalyst clearly accelerates the acylation rate and allows to improve slightly the yield of ketones (Scheme I). Such an influence of copper salts on the acylation of organomanganese chloride in THF has already been reported[2c].

Scheme I: Preparation of Elsholtzione **3** and Naginata Ketone **4**.



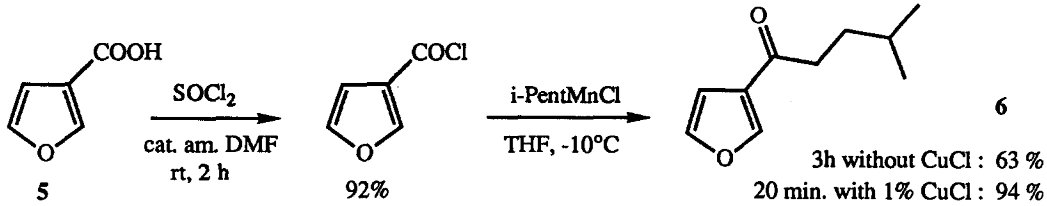
a / KOH aq , Reflux, 2h and H_3O^+.
b / $SOCl_2$, 1% DMF, CH_2Cl_2, rt, 2h.

3h, no CuCl : 86 %
20 min., 1% CuCl : 90 %

3h, no CuCl : 54 %
20 min., 1% CuCl : 68 %

As shown in Scheme II, perilla ketone **6** was prepared in excellent yield (94%) by acylation of isopentyl manganese chloride with 3-furoic acid chloride, easily obtained by treating commercial 3-furoic acid **5**[9] with thionyl chloride. In the presence of a catalytic amount of cuprous chloride, the acylation reaction is, as above, much more rapid and the yield significantly higher.

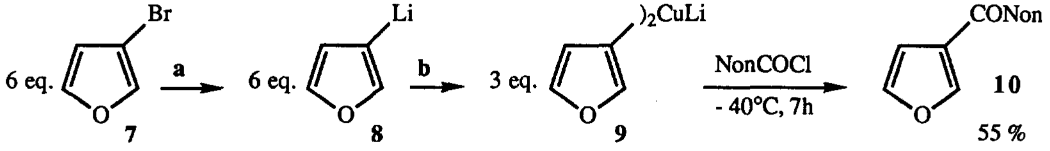
Scheme II: Preparation of Perilla Ketone **6** from 3-Furoic Acid.



3-Acyl-furans can be obtained according to another strategy, the acylation of a 3-furyl metal derivative. The major difficulty of such an acylation is related to the low stability of these organometallics (β-oxygen elimination), which must be prepared and used at low temperature (-80°C to -50°C). In fact, copper[10] and zinc[11] derivatives as well as tin compounds in the presence of palladium[5c, 6h] have been used, but the furyl ketones are obtained in moderate yields (from 10 to 60% based on the starting furyl lithium).

The copper route, described in Scheme III, was reported by Kato[10]. Furyl ketone **10** was prepared in 55% yield from decanoyl chloride. However, it should be pointed out that the furyl ketone **10** was obtained in only 9% yield from the starting furyl lithium **8** since **9** must be used in a large excess (3 equiv.). Moreover, it is necessary to prepare **8** by lithium-bromide exchange from **7** by using 2 equivalents of tert-butyllithium. Indeed, the tert-butyl bromide formed during the preparation of **8** must be eliminated from the reaction mixture, because it can react with the furyl cuprate **9**.

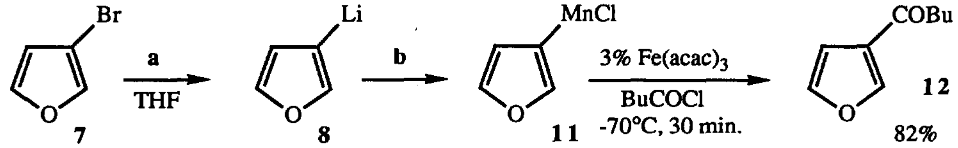
Scheme III: Acylation of Lithium 3-Furyl Cuprate **9**.



a / 12 equiv. t-BuLi , THF, -78°C, 30 min.; b / 3 equiv. CuI;Me_2S, -50°C. (9% from bromofuran)

In comparison, the organomanganese route depicted in Scheme IV presents some obvious advantages. Furyl lithium **8** was prepared by treating 3-bromofuran **7** with one equivalent of butyllithium instead of 2 equiv. of tert-butyllithium as above (Scheme III). Indeed, the presence of butyl bromide is tolerated[12] during the subsequent lithium-manganese exchange which was performed by adding one equivalent of the ate complex $MnCl_2$;2 LiCl as a THF solution. Acylation of the furyl manganese chloride **11** by pentanoyl chloride (equimolar amount), in the presence of a catalytic amount of iron (III) acetylacetonate[13], gave the expected furyl ketone **12** in good yield (82%). Interestingly, only one equivalent of the starting organolithium **8** is used instead of six equivalents with the cuprate procedure (Scheme III).

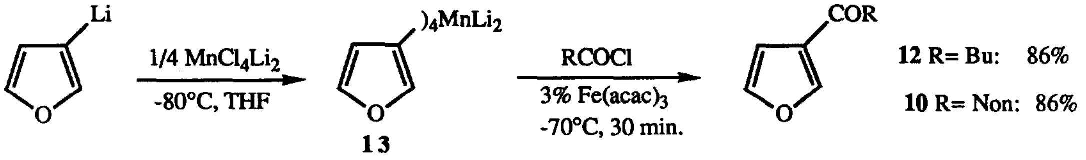
Scheme IV: Acylation of 3-Furyl Manganese Chloride.



a / BuLi, -78°C, 30 min. ; b / $MnCl_4Li_2$, -80°C, 30 min.

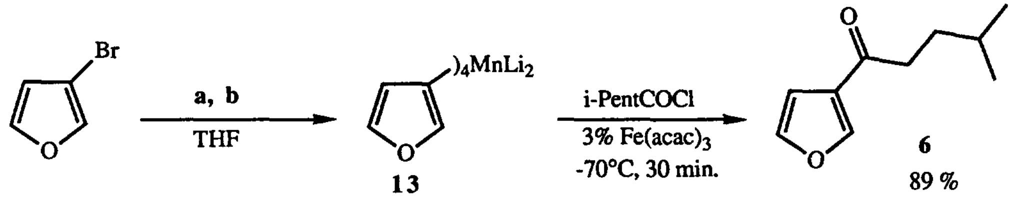
The tetrafurylmanganate **13** can also be used successfully. The ketones **10** and **12** were thus obtained in excellent yield (Scheme V). It is worthy of note that the four furyl groups bonded to manganese react[14].

Scheme V: Preparation of 3-Acyl Furans by Acylation of Tetrafurylmanganates.



According to this one-pot procedure, perilla ketone **6** was synthesized in 89% yield (Scheme VI).

Scheme VI: Preparation of Perilla Ketone **6** from 3-Bromo Furan.



a / 1 equiv. BuLi, -78°C, 30 min. ; **b** / 0.25 equiv. $MnCl_4Li_2$, -80°C, 30 min.

In conclusion, we have shown that organomanganese reagents allow to prepare 3- and 2-acylfurans, under mild conditions, in excellent yields. They compare very favorably to the other organometallic compounds used until now (Cd[6a], Zn[14], Sn[5c, 6h], Cu[10], Mg[5d]).

The use of iron (III) acetylacetonate as catalyst should be emphasized since it allows to acylate successfully, at low temperature, the organomanganese reagents **11** and **13** which are not stable above -50°C.

Typical procedure:

Preparation of perilla ketone from 3-furoyl chloride:

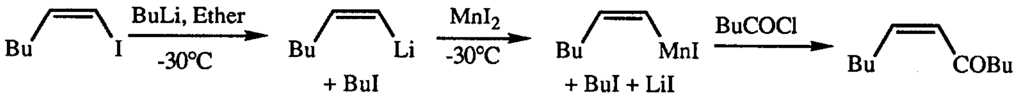
A solution of isopentyl magnesium bromide (52 mmol) in tetrahydrofuran was added to a solution of the "ate" complex $MnCl_2$; $2LiCl$[15] (52 mmol) at -10°C. After stirring during 30 min. at 0°C, the mixture was cooled at -10°C then CuCl (1%, 0.5 mmol) and 3-furoyl chloride (50 mmol) were added successively. The reaction mixture was allowed to warm to room temperature and stirred for 20 min. then hydrolysed with 80 ml of 1M HCl at -10°C. After usual work-up, the perilla ketone was isolated by distillation (97°C/10 torr) in 94% yield.

Preparation of perilla ketone from 3-bromofuran:

A solution of n-butyllithium in hexane (52 mmol) was added dropwise to a solution of 3-bromofuran (55 mmol) in tetrahydrofuran (100 ml) at -70°C. After 30 min., 0.25 equiv. of the "ate" complex $MnCl_2$; $2LiCl$[15] (as a THF solution; 12.5 mmol/50 ml) was added dropwise at -80°C. The reaction mixture was stirred for 30 min., then, iron(III) acetylacetonate (3%, 1.5 mmol) and isohexanoyl chloride (50 mmol) were successively added at -70°C. Stirring was continued for 30 min. at room temperature. The reaction mixture was treated as above and the perilla ketone was obtained in 89% yield.

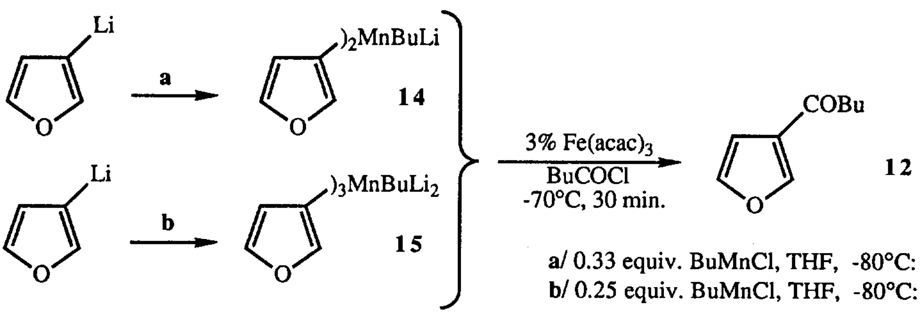
Notes and References.

1. Organomanganese (II) Reagents XXIV. For Part XXIII see: Cahiez, G.; Laboue, B. *Tetrahedron Lett.*, **1992**, in press.
2. a/ Cahiez, G. *L'actualité chimique,* September **1984**, 24. b/ Cahiez, G.; Laboue, B. *Tetrahedron Lett.*, **1989**,*30*, 3545-3546. c/ Cahiez, G.; Laboue, B. *Tetrahedron Lett.*, **1989**, *30*, 7369-7372. See also ref. 1.
3. For review, see: *The total synthesis of natural products*; ApSimon, J. Ed; John Wiley and sons, Inc.: New York; Vol. 2, 1973; pp. 159-165; Vol. 4, 1981; pp. 557-562.
4. **Elsholtzione** : a/ Reichstein, T.; Zschokke, H.; Goerg, A. *Helv. Chim. Acta,* **1931**, *14*, 1277-1282. b/ Finan, P. A.; Fothergill, G. A. *J. Chem. Soc.*, **1963**, 2723-2727. c/ Finan, P. A.; Fothergill, G. A. *J. Chem. Soc.*, **1963**, 2728-2731. d/ Cazes, B.; Julia, S. *Synth. Commun.*, **1977**, *7*, 113-117.
5. **Naginata ketone** : a/ Fujita, Y.; Ueda, T. *Chem. and. Ind.*, **1960**, 236. b/ Finan, P. A.; Fothergill, G.A. *J. Chem. Soc.*, **1962**, 2262-2266. c/ Ueda, T.; Fujita, Y. *Chem. and Ind.*, **1962**, 1618-1619. d/ Buechi, G.; Kovats, E. SZ.; Enggist, P.; Uhde, G. *J. Org. Chem.*, **1968**, *33*, 1227-1229. e/ Pillot, J. P.; Benneteau, B.; Dunoguès, J.; Calas, R. *Tetrahedron Lett.*, **1980**, *21*, 49, 4717-4720.
6. **Perilla ketone** : a/ Matsuura, T. *Bull. Chem. Soc. Japan,* **1957**, *30*, 430. b/ Arata, Y.; Achiwa, K. *Ann. Rep. Fac. Pharm.*, **1958**, *8*, 29. c/ Kondo, K.; Matsumoto, M. *Tetrahedron Lett.*, **1976**, *17*, 4363-4366. d/ Zamojski, A.; Kozluk, Y. *J. Org. Chem.*, **1977**, *42*, 1089-1090. e/ Kitamura, T.; Kanakami, Y.; Imagawa, T.; Kawanishi, M. *Synth. Commun.*, **1977**, *7*, 521-528. f/ Abdulla, R. F.; Fuhr, K. H. *J. Org. Chem.*, **1978**, *43*, 4248-4250. g/ Brown, H. C.; Srebnik, M.; Bakshi, R. K.; Cole, T. E. *J. Am. Chem. Soc.*, **1987**, *109*, 5420-5426. h/ Bailey, T. R. *Synthesis,* **1991**, 242-243.
7. Burness, D. M. *Org. Syntheses*, Coll. IV, **1963**, 628-630 and 649-652.
8. In ether, the ketones **3** and **4** were prepared in lower yields. Ketone **3**; from i-BuMnBr: 62% and from i-BuMnI: 77%. Ketone **4**; from $Me_2C=CMnBr$: 46% and from $Me_2C=CMnI$: 61%.
9. This acid can be easily prepared by carbonation of 2-furyl lithium: Fukuyama,Y.; Kawashima, Y., Miwa, T.; Tokoroyama, T. *Synthesis,* **1974**, 443-444.
10. Kojima,Y.; Wakita, S.; Kato, N. *Tetrahedron Lett.*, **1979**, *20*, 4577-4580.
11. Ennis, D. S.; Gilchrist, T. L. *Tetrahedron*, **1990**, *46*, 2623-2632.
12. Organomanganese reagents can even be prepared by lithium-manganese exchange in the presence of the very reactive alkyl iodides: Cahiez,G.; Friour, G., unpublished results.



80 % overall yield

13. Without $Fe(acac)_3$ as catalyst, the ketone **12** was obtained in only 41% yield. In the presence of 2% CuCl, the yield is still lower (31%).
14. The ketone **12** was also prepared successfully from unsymmetrical lithium organomanganates such as the di- and tri-furyl butyl manganates **14** and **15**.



a/ 0.33 equiv. BuMnCl, THF, -80°C: 90%
b/ 0.25 equiv. BuMnCl, THF, -80°C: 95%

The yields of the reactions are based on the starting bromofuran. Respectively 3 (**14**) or 4 (**15**) equivalents of pentanoyl chloride are required since the butyl group is also acylated.

15. The preparation of $MnCl_4Li_2$ in THF has already been described: Cahiez, G.; Alami, M. *Tetrahedron*, **1989**, *45*, 4163-4176.

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