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Ruthenium Tetroxide Catalyzed Oxidations of 3-Alkyl-4-(2-furyl)-4-oxobutanenitriles: Synthesis of Methyl 2-Alkyl-3-cyanopropanoates.

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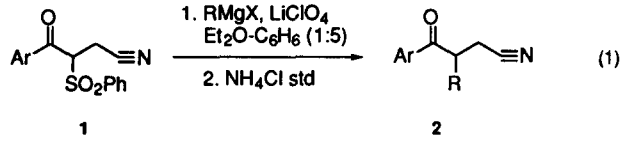
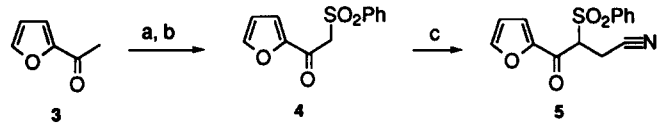
Abstract: Furan ring in 3-alkyl-4-(2-furyl)-4--oxobutanenitriles is completely oxidized by the $RuCl_3$-KIO_4 couple to efficiently afford, after esterification, methyl 2-alkyl-3-cyanopropanoates in good yields.

The direct introduction of alkyl frameworks at 2 position of alkanoic acids and esters is nowdays a well established procedure, that is usually carried out by a simple alkylation of ester enolates.[1] However, the search for alternative approaches directed towards the synthesis of 2-functionalized acids and derivatives is still a matter of interest, expecially when chemoselectivity problems must be overcome. Recenly we have reported that direct substitution of the phenylsulfonyl group is observed during the reaction of Grignard reagents with 3-phenylsulfonyl-4-oxoarenebutanenitriles in the presence of lithium perchlorate (eq.1).[2]

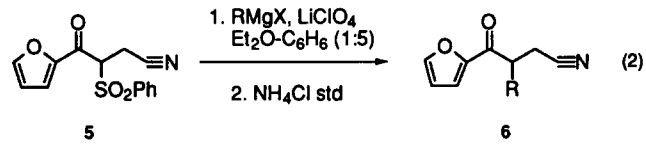


1 2 (1)

The reaction is conducted at room temperature in a diethyl ether-benzene mixture (1:5) and primary, secondary and functionalized magnesium reagents can be used for this procedure. Although the cyano group is unaffected by these conditions, a substantial lack of reactivity is observed when the aryl group in ketonitriles **1** is substituted by alkyl or alkoxy groups. In order to circumvent this drawback, we decided to exploit other heteroaromatic systems that could conserve good reactivity, but act as precursors for other useful functionalities. In this context, the furan ring has shown a wide array of cleavage opportunities[3] and therefore we have focused our attention on its utilisation. 3-Phenylsulfonyl-4-(2-furyl)-4-oxobutanenitrile **5** was prepared using standard conditions (Scheme 1) and treated with different Grignard reagents in the presence of 1 equivalent of lithium perchlorate in a ether-benzene mixture (1:5) at room temperature (eq. 2).

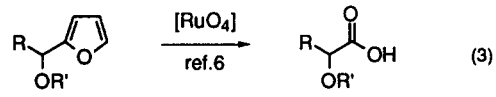


Scheme 1 : (a) Br_2 , dioxane-ether, 20°C, 82%; (b) $PhSO_2Na$, DMF, 20°C, 90%; (c) NaH, $BrCH_2CN$, THF, 20°C, 80%

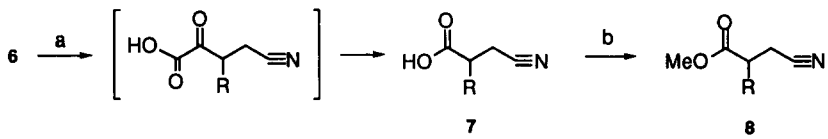


The results (Table), show that the furan ring shows an equivalent ability to the other benzene moieties to favour the substitution process of the phenylsulfonyl group by organomagnesium reagents.[4]

Ruthenium tetroxide is a powerful oxidizing reagent, and is capable of a complete demolition of aromatic rings affording carboxylic acids.[5] The furan nucleus is particularly oxidizable by ruthenium tetroxide, and this procedure has been profitably used on chiral 2-furylcarbinols that can thus be converted into 2-hydroxy carboxylic acids (eq. 3).[6]



3-Alkyl-4(2-furyl)-4--oxobutanenitriles **6** hexhibit a peculiar and previously unobserved behaviour towards oxidation with ruthenium tetroxide. In this case the carbon skeleton of the furan ring is completely removed under these oxidative conditions, affording the corresponding 2-alkyl-3-cyanopropanoic acids **7** (Scheme 2).



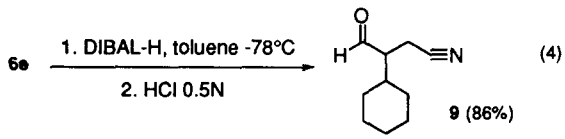
Scheme 2 : (a) 3% $RuCl_3$ $3H_2O$, 8 equiv. KIO_4, CH_3CN-CH_2Cl_2-H_2O (2;2:3), 20°C; (b) MeOH, Amberlyst 15, 20°C.

A possible intermediate in this cleavage pathway is the corresponding α-ketoacid that is further oxidised to the acid **7**.[7] Furylketonitriles **6** have been oxidised using 3% mol. ruthenium trichloride as catalyst together with varying amounts of potassium periodate[8] depending on the substrate (Table). The original solvent system (carbon tetrachloride, acetonitrile,water in a ratio 2:2:3)[5b] has been sightly modified replacing carbon tetrachloride with dichloromethane and this gives better results in several cases.[9]

Table. Reaction between furylketonitrile **5** with Grignard reagents in Et_2O-C_6H_6 (1:5) in the presence of $LiClO_4$, followed by oxidation with $RuCl_3/KIO_4$ couple and methyl esterification.

Entry	RMgX	Substitution Product	yield (%)	Oxidation Product	Equiv. KIO_4	yield (%)
1	*n*BuMgCl	**6a**	75	**8a**	8	73
2	EtMgBr	**6b**	68	**8b**	9	70
3	MeMgCl	**6c**	72	**8c**	11	68
4	*s*BuMgBr	**6d**	74	**8d**	7	77
5	1-C_6H_{13}MgBr	**6e**	78	**8e**	8	80
6	2-C_5H_{11}MgCl	**6f**	68	**8f**	11	70
7	*c*C_6H_{11}MgBr	**6g**	70	**8g**	12	65
8	$BnO(CH_2)_4MgBr$	**6h**	78	**8h**	10	72
9	Me_3SiCH_2MgCl	**6i**	75	**8i**	8	77

Unfortunately, this oxidative procedure is not effective with arylketonitriles of type **1** since the presence of a carbonyl group with its electron withdrawing character, has a deleterious effect on the oxidation.[5a,6c] Conversely, the furan ring is oxidised even in the presence of an adjacent carbonyl group, probably because of its electron rich nature. When short chain (methyl, ethyl) alkyl groups are introduced by the organomagnesium reagent, the corresponding acids **7** are often too soluble in water to be efficiently isolated. Therefore, carboxylic acids **7** were directly converted into methyl esters using Amberlyst 15 ion exchange resin in methanol.[10] The three step procedure (**5** to **8**) ultimately represents an efficient entry to 2-alkyl-3-cyanopropanoates and allow circumvention of the reduced reactivity of the corresponding 2-phenylsulfonyl derivatives **1**. The capability of the ester group to be converted into an aldehyde using different reducing agents greatly expands the synthetic significance of the present procedure. In this context it is worth noting that the ester group can be reduced to the aldehyde function with surprising chemoselectivity using DIBAL-H as a reducing agent despite the known sensibility of the cyano group to this reagent (eq. 4) .[11]



(4)

In conclusion, we have devised an easy and efficient entry to methyl 2-alkyl-3-cyanopropanoates **8** by means of a substitution-oxidation procedure starting from 3-phenylsulfonyl-4-(2-furyl)-4-oxobutanenitrile **5**[12] Although some esters **8** may be prepared by conventional methods[13] this procedure represents an alternative route to their synthesis. Further investigations on the mechanism and synthetic potentialities of this procedure are in progress in our laboratory.

Acknowledgments. The authors thank University of Camerino for the financial assistance.

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4. As pointed out in ref 2, the corresponding 2-pyridyl derivative is completely inert towards the substitution process.
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7. Similar behaviour has been observed during the oxidation of terminal alkynes with RuO_2/NaOCl : Gopal, H.; Gordon, A. J. *Tetrahedron Lett.* **1971**, 2941.
8. Reactions conducted using dichloromethane are faster than those in carbon tetrachloride. Furthermore, lesser amounts of ruthenium trichloride and potassium periodate are required using dichloromethane.
9. Periodic acid has been described (ref.5b) as a better oxidant than periodate salts, but in our hands it gave only disappointing results probably because of the acid-sensitivity of the furan ring.
10. Petrini, M.; Ballini, R.; Marcantoni, E.; Rosini, G. *Synth. Commun.* **1988**, *18*, 847.
11. Fatiadi, A. J. In *The Chemistry of Triple-bonded Functional Groups*, Patai, S.;Rappoport, Z. Eds. J. Wiley, Chichester, 1983, Vol. 2, p. 1057.
12. *Typical experimental procedures are illustrated for the following compounds: 3-Butyl-4-(2-furyl)-4-oxobutanenitrile* **6a** : Furylbutanenitrile **5** (0.29g, 1mmol) was dissolved in dry benzene (25 mL) and then ether (5 mL) and lithium perchlorate (0.1g, 1mmol) were successively added under N_2 at room temperature. The mixture was stirred for 15 min and then butylmagnesium chloride (4 mmol, 1M in THF) was added dropwise at room temperature and the mixture was stirred at this temperature for 1h. Subsequently, saturated amonium chloride (10 mL) was poured into the mixture. After extraction with dichloromethane (3 x 25 mL) the organic phase was washed with saturated sodium chloride (10 mL) and dried over magnesium sulfate. Column chromatography (hexane/ethyl acetate 7:3) afforded 0.153g. (75% yield) of the pure product **6a** as an oil. ν_{MAX}/cm^{-1} 2220, 1650; δ_H (300 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.7 Hz), 1.25-1.27 (4H, m), 1.67-1.88 (2H, m), 2.58 (1H, dd, *J* 7.1, 16.9 Hz), 2.71 (1H,dd, *J* 7.1,16.9 Hz) 3.55-3.61 (1H, m), 6.57-6.60 (1H, m), 7.27-7.29 (1H, m), 7.63-7.64 (1H, m); *m/z* 205(M^+), 149, 95. *Methyl 2-Butyl-3-cyanopropanoate* **8a** : Compound **6a** (0.3g, 1.46 mmol) was dissolved in a mixture of dichloromethane-acetonitrile-water (4:4:6 mL) followed by addition of potassium periodate (2.39g, 10.4 mmol). After 15 minutes, ruthenium trichloride trihydrate (10 mg) was added and the black suspension was strirred for 16 h at room temperature Dichloromethane (40 mL) was then added and the aqueous phase was separated. The organic phase was dried over magnesium sulfate and evaporation of the solvent gave the crude acid which was dissolved in methanol (30 mL). Amberlyst 15 (1.0g) was added and the suspension was stirred for 12 h at room temperature. The resin was then filtered off and methanol was removed at reduced pressure to afford the crude ester which was purified by column chromatography using hexane-ethyl acetate (4:1) as eluent. giving compound **8a** as an oil (0.18g, 73%). ν_{MAX}/cm^{-1} 2240, 1750; δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.0 Hz), 1.24-1.35 (4H, m), 1.65-1.76 (2H, m), 2.54 (1H, dd, *J* 6.9, 16.7 Hz), 2.64 (1H, dd, *J* 6.9, 16.7 Hz), 2.69-2.76 (1H, m), 3.74 (3H, s); δ_C 14.25, 19.77, 22.82, 20.10, 31.52, 41.95, 52.76, 118.28, 173.74; *m/z* 113, 98, 57, 41 .
13. Alkylation of ester enolates with bromoacetonitrile generally leads to the synthesis of compounds **8** in modest yields: a) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277; b) Koskinen A. M. P.; Rapoport, H. *J. Org. Chem.***1989**, *54*, 1859. A radical induced addition of alkyl groups to methyl fumarate mononitrile has been also proposed: c) Giese, B.; Lachhein, S. *Chem. Ber.* **1985**, *118*, 1616.

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