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SHORT-STEP SYNTHESIS OF NAPROXEN. REGIOSELECTIVE FRIEDEL-CRAFTS REACTION OF 2-CHLORO-2-ALKYLTHIO-PROPIONATES[1)]

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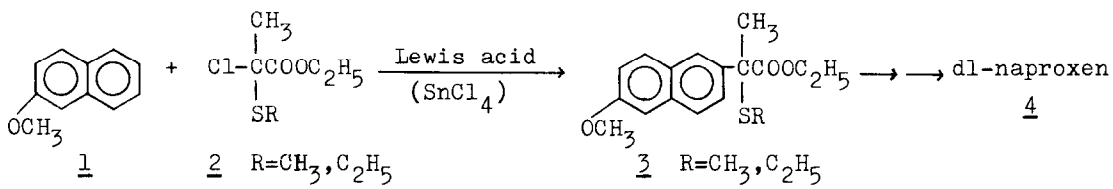
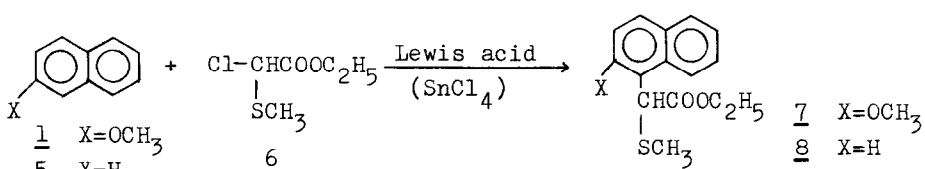
Summary: 2-(6-Methoxy-2-naphthyl)propionic acid(4), dl-naproxen, was conveniently prepared by the regioselective reaction of alkyl 2-chloro-2-alkylthio-propionate (2) and 2-methoxynaphthalene (1) in good yield. This Friedel-Crafts reaction was found to be applicable to the other electron-rich aromatics.

As one of many synthetic applications of α-chlorosulfides,[2)] Tamura and his colleague have accomplished the preparation of arylacetates by the Friedel-Crafts reaction of ethyl 2-chloro-2-methylthio-acetate (6), which indicates much more reactivity than ethyl 2-chloro-acetate by the introduction of the methylthio group.[3)] We report in this paper one modified application of their work to a preparation of 2-(6-methoxy-2-naphthyl)propionic acid (4), d enantiomer of which, naproxen, is well-known compound as one of potent antiinflammatory agents.[4)]



1 2 R=CH3,C2H5 3 R=CH3,C2H5 4



1 X=OCH3 5 X=H 6 7 X=OCH3 8 X=H

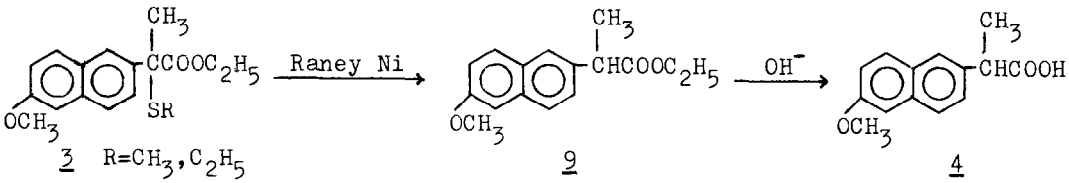
Firstly, we tried the reaction between alkyl 2-chloro-propionate and 2-methoxynaphthalene (1) for the preparation of 4, but there was no reaction under ordinary Friedel-Crafts reaction condition because of low reactivity of 2-chloro-propionate. Secondly, it had been found that the attack of 6 occurs

into α-position of naphthalene (5) in Tamura's work, but we tried the reaction of 6 with 1 with expect of some change of regioselectivity, because regioselectivity of Friedel-Crafts reaction of 1 is often found to change from that of 5 itself, and we unfortunately obtained undesired ethyl methylthio-(2-methoxy-1-naphthyl)-acetate (7).[5] However, at last the reaction of ethyl 2-chloro-2-alkylthio-propionates (2) and 1 luckily gave ethyl 2-alkylthio-2-(6-methoxy-2-naphthyl)propionates (3), which are adequately regioselective compounds for the synthesis of naproxen. This change of regioselectivity perhaps results from the bulkiness and/or the carbonium ion stabilizing ability of methyl group of 2.

The following procedure for the preparation of 3 is representative.

In 8.0 g of carbon tetrachloride, 1.48 g (1.05 eq moles) of ethyl 2-methylthio-propionate was dissolved, and 1.48 g (1.16 eq moles) of N-chlorosuccinimide was added thereto at 20°C. Stirring was continued for further 1.5 hours at the same temperature. The reaction mixture was promptly filtered, and washed with 6.0 g of carbon tetrachloride, whereby the succinmide floating in a form of crystals was filtered off. The carbon tetrachloride solution of ethyl 2-chloro-2-methylthio-propionate (2 : R=CH_3) thus obtained was dropwise added at from 25° to 30°C to a solution which was prepared by firstly dissolving 1.50 g (1.00 eq mole) of 2-methoxynaphthalene (1) in 25 g of methylene chloride and then adding 2.65 g (1.07 eq moles) of stannic chloride. After the completion of the addition, stirring was continued for 45 minutes at the same temperature. The results were poured into ice-water, and the organic layer was washed with water and concentrated under reduced pressure, whereupon 2.75 g of yellowish oily substance was obtained. A portion of this oily substance was subjected to thin layer chromatography to give colorless oily substance. And it was found to be obtained ethyl 2-methylthio-2-(6-methoxy-2-naphthyl)propionate (3 : R=CH_3),[6] in 72 % yield.

The intermediate 3 was desulfurized by ordinary methods, such as Raney nickel, zinc dust with acetic acid, or sodium alkanethiolate, giving ethyl 2-(6-methoxy-2-naphthyl)propionate (9) in more than 95 % yield.[6] And hydrolysis



3 R=CH_3,C_2H_5 9 4

of 9 with alkaline solution gave dl-naproxen (4) in more than 95 % yield.[6]

There have been two serious drawbacks of conventional methods for the synthesis of naproxen; (I) poor positional selectivity in the preparation of key intermediates such as 2-acetyl-6-methoxynaphthalene,[7] and (II) many synthetic steps needed from starting material, 2-methoxynaphthalene (1), to dl naproxene (4).[8] Both drawbacks will be conquered in the present method, and which is provided by the good reactivity of 2 resulted from an introduction of alkylthio group, and by the positional selectivity in the reaction of 2 and 1.

Table 1. Friedel-Crafts reaction of aromatics with 2 or 6.*

ArH + 2 or 6 —cat.→ Ar—C(CH3)(SR)—$COOC_2H_5$ or Ar—$CH(SCH_3)COOC_2H_5$

ArH	2 or 6	cat.	regioselectivity	yield(%)	
CH_3O-Ar	2 (R=CH_3)	$SnCl_4$	p-	77	
	2 (R=C_2H_5)	$TiCl_4$	p-	80	
	2 (R=CH_3)	$AlCl_3$	p-	50	
	6	$TiCl_4$	p- : o- = 5 : 2	98	ref. 3
HO-Ar	2 (R=C_2H_5)	$TiCl_4$	p-	83	
	6	$SnCl_4$	p- : o- = 2 : 1	90	
S	2 (R=CH_3)	$SnCl_4$	2-	85	
	2 (R=C_2H_5)	$TiCl_4$	2-	70	
	6	$TiCl_4$	2-	59	ref. 3
	2 (R=CH_3)	$SnCl_4$	p-	~5**	
	6	$SnCl_4$	p-	quant.	ref. 3

* ArH:2 or 6: cat. ≒ 1:1:1; reaction temp. 0°~rt; reaction time 10~90 min.
** Main product was tar.

Further examples of the application of this Friedel-Crafts reaction of 2 were listed up in Table 1. The regioselective character is more improved in the reaction of 2 with anisol or phenol than in that of 6. And the yield of the adduct of this Friedel-Crafts reaction of 2 with isobutylbenzene is much less than that of 6. Thus, the present reaction is seemed to be applicable to electon-rich aromatics and to be rather regioselective. Also these adducts can be easily desulfrized and then hydrolyzed in the same manner as dl-naproxen (4) to give various arylpropionic acids.

References and Notes

1. A part of Japan Laid-Open Patent, 57-118554 (1982).
2. H. Gross and E. Höft, Angew. Chem., 79, 358 (1969); K. Arai, J. Synth. Org. Chem. Japan, 39, 374 (1981).
3. Y. Tamura, H. Shindo, J. Uenishi, and H. Ishibashi, Tetrahedron Lett., 21, 2547 (1980); Y. Tamura, H. D. Choi, H. Shindo, and H. Ishibashi, Chem. Pharm. Bull., 30, 915 (1982).
4. I. T. Harrison, B. Leis, P. Nelson, W. Books, A. Roszkowski, A. Tomolonis, and J. H. Fried, J. Med. Chem., 13, 203 (1970).
5. α-Methylation of 7 by NaH/DMF and CH_3I was rather hard, which yielded the recovered 7 (25%), propionate (10) (15%), which was the stereoisomer of 3, acrylate (11) (20%), and so on. Both of 10 and 11 were hydrogenated with Raney Ni to give the same stereoisomer of 9. These are considered to result from the steric hyndrance of the neighboring methoxy group of 7.
6. (3: R=CH_3) NMR($CDCl_3$):δ 1.27(3H,t,7Hz),1.88(3H,s),1.97(3H,s),3.89(3H,s),4.27 (2H,q,7Hz),7.05~7.95(6H,m). MS(m/e):M^+=304.1151(Calcd. $C_{17}H_{20}O_3S$=304.1133). (9) mp 50~52°C. NMR($CDCl_3$):δ 1.19(3H,t,7Hz),1.56(3H,d,7Hz),3.83(1H,q,7Hz), 3.88(3H,s),4.12(2H,q,7Hz),6.9~7.8(6H,m). MS(m/e):M^+=258.1291(Calcd. $C_{16}H_{18}O_3$ =258.1256). (4) mp 156~157°C (Lit. mp 150~151°C in ref. 4).
7. 1-Acetyl-2-methoxynaphthalene is main product in the acetylation of 1 with acetyl chloride and $AlCl_3$ in CS_2, and even in nitrobenzene, yield of 2-acetyl-6-methoxynaphthalene is 45-48 %. R. B. Girdler, P. H. Gore, and J. A. Hoskins, J. Chem. Soc. (C), 181 (1966); Org. Synth., 53, 5 (1973).
8. Tsuchihashi et al. have recently reported an elegant method for the synthesis of α-arylalkanoic acids by the use of 1,2-rearrangement of the aryl group, but there are 6 steps from 2-methoxynaphtalene (1) to dl-naproxen (4) in their method. G. Tsuchihashi, K. Kitajima, and S. Mitamura, Tetrahedron Lett., 22, 4305 (1981).

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