Tetrahedron Letters No. 27, pp 2373 - 2376, 1974. Pergamon Press. Printed in Great Britain.

Novel Aspects of the Metalation of Heterocycles. Side-chain Metalation of Thiophen and Ring Metalation of Six-Membered Nitrogen Heterocycles

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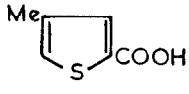
(Received in UK 6 May 1974; accepted for publication 30 May 1974)

The metalation of heterocycles has long been a powerful synthetic tool[1]. However it suffers certain limitations. In the 5-membered series (e.g. thiophen, furan etc.), metalation occurs exclusively at the α-position[2], side-chain metalation being unknown. In the 6-membered series (e.g. pyridine) either addition to the ring or side-chain metalation (e.g. of α- or γ-picoline) are preferred. We herein record our attempts to metalate the former series in the side-chain and the latter in the ring.

The action of various metalating agents on thiophens is recorded in the Table. With 3-methylthiophen, although the selectivity of the reagent seems to decrease with its increasing power (indicative of a change from thermodynamic to kinetic control) no evidence of side-chain metalation is observed. Similarly with 2-methylthiophen only the corresponding 5-carboxylic acid was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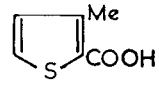
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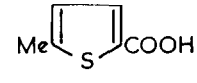
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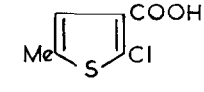
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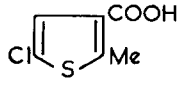
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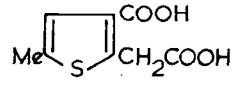
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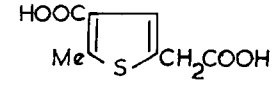
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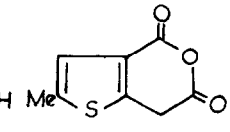
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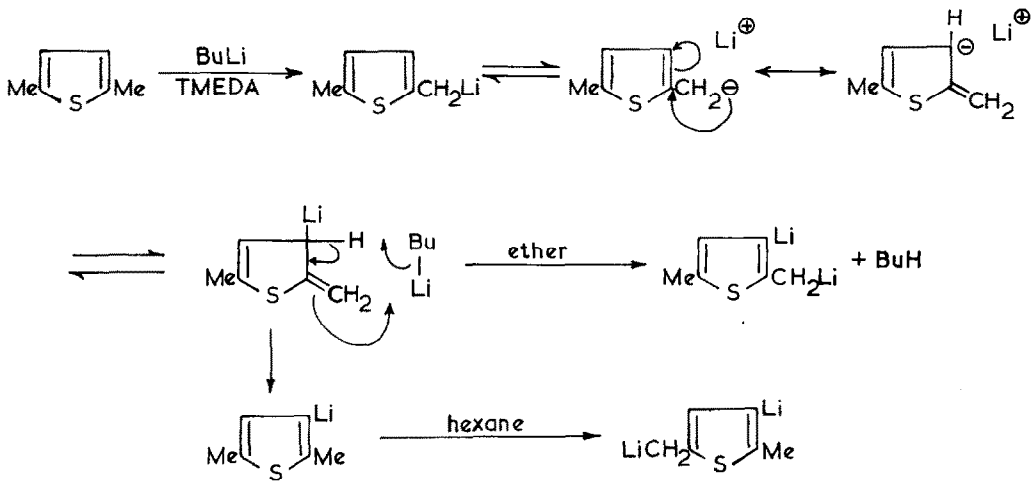
isolated using various reagents. In order to inhibit α-metalation, 2-chloro-5-methylthiophen was next examined. The 2-chloro substituent is insufficiently reactive to undergo ready halogen-metal interconversion with butyl lithium[3]. However, admixed with TMEDA this reaction occurs readily at 25° together with β-metalation at the more acidic 3-position. With LDIPA (which does not react with bromothiophens at -70° [4]) β-metalation occurs at low temperature in low

yield (surprisingly favouring the 4-acid) but at 25° both halogen-metal interconversion and β-metalation occur but no side-chain attack. Other products, probably due to ring-opening[6], accompany those reported from 2-chloro-5-methylthiophen.

Side-chain metalation was achieved by action of BuLi/TMEDA on 2,5-dimethylthiophen, to precipitate 15-20% yield of a dimetalated derivative. Carbonation of this derivative gave a mixture of two acids, readily separably by sublimation in vacuo giving the diacid (7) m.p. 219° and the anhydride (8) m.p. 178°. No mono-acid was isolated and the use of hexane instead of ether as solvent reversed the preference of metalation. We tentatively account for these results in the Scheme. With 2,5-dimethylfuran or 2-methylbenzothiophen a



Scheme

similar precipitation of metalated derivatives occurs to give products on carbonation which have not yet been fully characterised but appear to follow the same course.

Our strategy in the metalation of 6-membered heterocycles lay in the use of LDIPA in ether, a system known to show little tendency to add to multiple bonds. With pyridine, quinoline and isoquinoline dimers were obtained (see Table), best accounted for by formation of the α-lithio derivative which then adds to another molecule of the base. However a wide variety of trapping agents failed to intercept the α-lithio derivative. Good yields of the dimers

Table

Substrate	Temp (°C)	Time (hr)	Solvent	Metalating* agent	Total+ yield (%)	Product(s) ratio +
3-MT	0	0.5	Ether	BuLi	33	(1)+(2) 4.6 : 1 [a]
"	-70	0.5	Ether	BuLi/TMEDA	53	(1)+(2) 3.5 : 1
"	0	0.5	Ether	LDIPA	52	(1)+(2) 9 : 1
"	35	24	Ether	LDIPA	2	(1)+(2) 24 : 1
"	50	0.25	$(i\text{-}Pr)_2NH$	LDIPA	11.5	(1)+(2) 4 : 1
2-MT	25	0.5	Ether	BuLi	66	(3)
"	25	0.5	Ether	LDIPA	29	(3)
"	25	0.5	Ether	BuLi/TMEDA	66	(3)
2-Cl-5-MT	25	1	Ether	BuLi (1.5M) TMEDA (1.5M)	90	(3)+(4) 1.5 : 1
"	25	3	Ether	LDIPA	12	(3)+(4)+(5) 1:5.1:1.8
"	25	24	Hexane	LDIPA	v.low	mainly (5)
"	-70	1.5	Ether	LDIPA	4	(4)+(5) 1 : 1.8
2,5-DMT	25	3	Ether	BuLi (2M) TMEDA (2M)	14	(6)+(7) 9 : 1
"	25	2	Hexane	"	17	(6)+(7) 0.43 : 1
"	25	3	Ether	BuLi (2M) DABCO (2M)	v.low	(6)+(7) 9 : 1
"	25	24	Ether	LDIPA (2M)	-	
"	66	24	THF	LDIPA (2M)	v.low	
"	25	3	THF	BuLi (10M)	low	tarny products
Pyridine	25	1	Ether	LDIPA	17	2,2'-dipyridyl
"	35	1	Ether	LDIPA	26	"
"	-70	1	Ether	LDIPA/HMPTA	50	"
Quinoline	-70 to 35	1	Ether	LDIPA	10-15	2,2'-diquinolyl
"	-70	1	Ether	LDIPA/HMPTA	74	"
Iso-quinoline	0 to 35	1	Ether	LDIPA	10	1,1'-diisoquinolyl
"	-70	1	Ether	LDIPA/HMPTA	55	"
5-MP	0 to 35	1	Ether	LDIPA	30	(9)

* Unless stated otherwise 1M of reagent(s) was used per mole substrate.

\+ Determined by n.m.r. and corroborated by isolation of acids.

[a] Ramanathan and Levine[5] quote 3.2 : 1 after 2 hr reflux in ether (80%).

MT = methyl thiophen; MP = methylpyrimidine; TMEDA = tetramethylethylene-diamine; LDIPA = lithium diisopropylamide; DABCO = diazabicyclo{2,2,2}octane HMPTA = hexamethylphosphoric triamide.

were available by addition of HMPTA to the reaction mixture. 5-Methylpyrimidine, however gave no dimer but on treatment with LDIPA followed by benzophenone gave the adduct (9), m.p. 182° in 30% yield.

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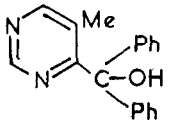
We thank Synthetic Chemicals Ltd. and Midland-Yorkshire Tar Distillers for a grant (to A.J.C.) and gifts of thiophens and Ciba-Geigy Ltd for a grant (to S.McN.).



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