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FRIEDEL-CRAFTS ACYLATION OF 1-TERT-BUTYLDIMETHYLSILYLPYRROLE, A VERY SHORT AND SIMPLE ROUTE TO 3-SUBSTITUTED PYRROLES.

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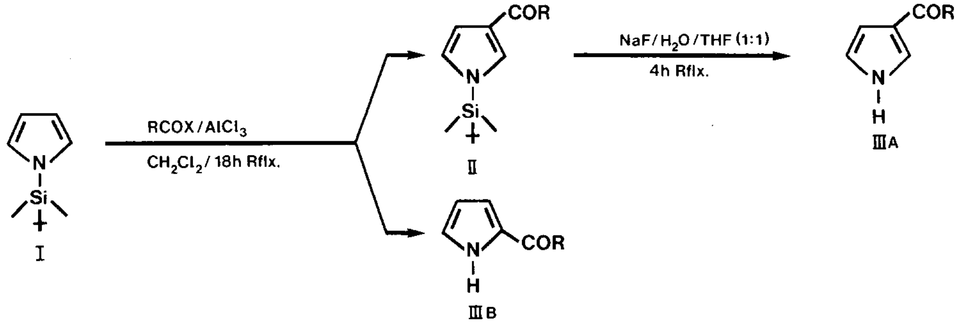
Abstract: 1-tert-Butyldimethylsilylpyrrole undergoes Friedel-Crafts acylation almost exclusively at β-position giving after sodium fluoride supported hydrolysis the 3-pyrroloketones.

The electrophilic substitution of pyrroles with soft electrophiles is orbital controlled and takes place at the α-position (2), whereas with hard electrophiles (like trimethylsilyl trifluoromethanesulfonate) this reaction becomes charge-electron density controlled and takes place predominantly at the β-position (3,4). The β-substitution of pyrroles with soft electrophiles was achieved either by applying meta-directing substituent at the 1- or 2-position of the pyrrole ring (5,6) or by using bulkier substituents on nitrogen (7). The bulkier silyl rests on nitrogen due to very easy removal appeared to serve best (8,9).

During the course of our studies devoted to the synthesis of 3-substituted pyrroles (2,3,10) we have found that the tert-butyldimethylsilyl (TBDMS) rest at nitrogen in pyrrole I (11) survives even the harsh Friedel-Crafts conditions, i.e., I can be directly acylated in the presence of aluminium chloride to give almost exclusively the β-isomer II. II can be quantitatively desilylated to III A by heating with sodium fluoride in THF/water (1:1) solution. This method seems to be the shortest one for synthesis of the 3-pyrroloketones (8,9,12).



In a standard procedure to a methylene chloride solution of the acylating agent (see Table I) 20% molar excess of aluminium chloride was added at 0-5°C followed by slow addition of an equimolar amount of I dissolved in the same solvent. Stirring was continued for 0.5 h, the cooling bath was removed and after another 0.5 h the reaction mixture was refluxed overnight and worked up as described for any typical Friedel-Crafts acylation. The GC analysis of the crude mixture before distillation showed almost always small amounts of the N-unsubstituted α-isomer III B to be present (Table I), what indicates partial cleavage of the TBDMS rest and subsequent acylation of the formed "free" pyrrole at the α-position. Better yields have been obtained when carboxylic anhydrides were used. The distillation in vacuum furnishes pure II which can be easily desilylated to III A by using equimolar amounts of sodium fluoride in THF/H_2O (1:1) (3 h reflux, 90% yield).

			GC%			II		III A		
	R	X	II	III A	III B	Yield %	b.p. (13)	m.p.	Tot. Yield	Ref.
1	CH_3	$OCOCH_3$	100	0	0	50	158-162/12	114-115	45%	6
2	Ph	Cl	87	0	13	46	158-160/0.001	100-101	42%	6
3	$PhCH_2$	Cl	83	3	13	63	90-92°(m.p.)	116-118	57%	13

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11) 24 h refluxing of the 1-potassium- or 1-lithiumpyrrole with molar amounts of TBDMS-Cl in THF furnishes I in 87% yield. Bp. 77-79/12 mm Hg. ^{1}H NMR (CDCl$_3$), δ: 6.69 (t,J=1.5Hz,2H,H_2H_5), 6.23 (t,J=1.5Hz,2H,H_3H_4), 0.81 (s,9H,CCH_3), 0.35 (s,6H,$SiCH_3$).
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13) ^{1}H NMR (CDCl$_3$), δ:
    II-1, 7.35 (t,J=1.6Hz,1H,H_2), 6.72-6.60 (m,2H,H_4,H_5), 2.39 (s,3H,CH_3CO), 0.88 (s,9H,CCH_3), 0.45 (s,6H,$SiCH_3$).
    II-2, 7.90-7.75 and 7.53-7.26 (m,5H,Arom.), 7.29 (t,J=1.6Hz,1H,H_2), 6.75 (d,J=1.6Hz,2H,H_4,H_5), 0.89 (s,9H,CCH_3), 0.45 (s,6H,$SiCH_3$).
    II-3, 7.32 (t,J=1.6Hz, 1H,H_2), 7.20 (s,5H,Arom.), 6.65 (d,J=1.6Hz,2H,H_4,H_5) 4.03 (s,2H,CH_2), 0.88 (s,9H,CCH_3), 0.45 (s,6H,$SiCH_3$).
    IIIA-3, 9.50-8.50 (br.s.1H,NH), 7.37-7.25 (m,1H,C_2H), 7.23 (s,5H,Arom.), 6.65 (t,J=1.8Hz,2H,H_4,H_5), 4.05 (s,2H,CH_2).

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