Tetrahedron Letters,Vol.24,No.33,pp 3455-3456,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

β-SUBSTITUTED PYRROLES VIA ELECTROPHILIC SUBSTITUTION OF N-TRIISOPROPYLSILYLPYRROLE[1].

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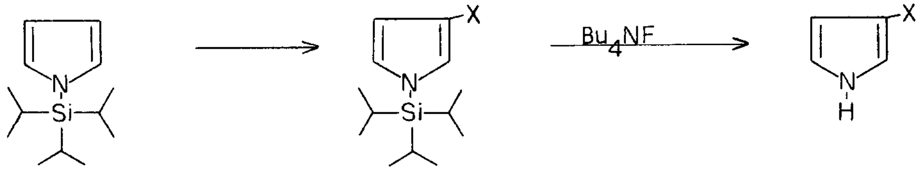
SUMMARY: N-Triisopropylsilylpyrrole undergoes predominant or exclusive kinetic electrophilic substitution at C-3, and the compounds obtained thereby, upon desilylation with tetra-*n*-butylammonium fluoride, give 3-substituted pyrroles in good overall yields.

Pyrrole undergoes predominant kinetic electrophilic substitution at the α-(2)-position. A long standing problem therefore has been to devise means of synthesising β-(3)-substituted pyrroles, and several processes, of variable efficiency, now exist which provide access to such compounds. These include the use of a deactivating 2-substituent (usually acyl) to direct the entry of an electrophile to the 4-(β)-position[2], the remarkably general acid induced isomerization of the readily available α-isomers[3], and the recently described direct 3-substitution of N-benzenesulfonylpyrrole with certain electrophiles[4]. Another approach to 3-substituted pyrroles is based on the utilization of a bulky group on nitrogen, such as a t-butyl[5] or a trityl moiety[6], to obstruct electrophilic attack at the α-position. Although substantial selectivity for C-3 is observed, this process has been of limited value because removal of the nitrogen substituent is difficult or the conditions required to effect N-dealkylation (e.g., Na/MeOH/NH_3) are incompatible with the survival of many functional groups. The concept is nevertheless a valid one and a sterically demanding, but easily removable, stable, N-substituent would have considerable synthetic value. This communication shows that the triisopropylsilyl moiety meets all of these requirements.



1 2 3

CPK models of N-triisopropylsilylpyrrole (1)[7], prepared in 73% yield from pyrrole and triisopropylsilyl chloride (NaH/DMF/0° to R.T.), show that both α-positions of the pyrrole nucleus are highly hindered. The reaction of this compound with N-Bromosuccinimide (1 equiv./THF/-78 to -20°) occurred rapidly and gave a mixture (*ca.*, 85:15) of monobrominated pyrroles in 74% isolated yield. The pmr ($CDCl_3$) spectrum of the major component showed, in addition to the absorptions for the *i*-propyl groups, three one proton double doublets at δ 6.29(H-4), 6.67(H-5) and 6.72(H-2) with $J_{2,4}$= 1.4 Hz., $J_{2,5}$= 2.2 Hz., and $J_{4,5}$= 2.8 Hz. uniquely consistent with that expected for 1-triisopropylsilyl-3-bromopyrrole (2, X = Br). This product mixture is indubitably the result of kinetic control since 2-bromopyrroles are reported to be stable under these reaction conditions[8], a fact which was confirmed in this case with independently prepared 1-triisopropylsilyl-2-bromopyrrole. The enhanced selectivity for the β-position is clearly of steric origin, because Ntrimethylsilylpyrrole was brominated essentially exclusively at C-2 with N-bromosuccinimide.

Other electrophiles also reacted with 1 under mild conditions. Thus, with ethoxalyl chloride/pyridine (3 equiv./CH_2Cl_2/-20° to R.T./48 h.), *p*-toluenesulfinyl chloride/pyridine (3 equiv./CH_2Cl_2/0°/2 h.) and cupric nitrate (1.6 equiv.) in acetic anhydride (R.T./ 2 h.) the 3-ethoxalyl(2, X = $COCO_2Et$; oil), 3-*p*-toluenesulfinyl (2, X = $SOC_6H_4CH_3$; mp 96°) and 3-nitro (2, X = NO_2; oil) derivatives were formed effectively exclusively (>95%) and were isolated in 70, 40 and 80% yields, respectively. The products of the first two reactions are those of kinetic control[9,10], and it is probable that the 3-nitro compound is also.

As expected, the removal of the N-silyl group was accomplished easily with tetra-*n*-butylammonium fluoride (1 equiv./THF/R.T./5 min.). After silica gel chromatography (hexane-EtOAc, 4:1), 3-bromopyrrole (3, X = Br; δ 6.15(dd, H-4), 6.62(dd, H-5), 6.68(dd, H-2) with $J_{2,4}$ = 1.5 Hz., $J_{2,5}$ = 2.2 Hz., and $J_{4,5}$ = 2.9 Hz.) was isolated as an unstable oil in 65% yield. Similarly, 3-ethoxalylpyrrole (3, X = $COCO_2Et$; mp 89°) and the known 3-*p*-toluenesulfinyl (3, X = $SOC_6H_4CH_3$)[10] and 3-nitro (3, X = NO_2)[11] pyrroles were each obtained in virtually quantitative yield.

In addition to impeding the entry of an electrophile at C-2, the N-triisopropylsilyl group greatly improves the stability of some of the pyrroles. For example, whereas 3-bromopyrrole is very unstable, the N-silylated derivative is indefinitely stable under normal laboratory conditions.

The results described herein have a large number of synthetic ramifications.

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Received in USA 26 May 1983)