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AN APPLICATION OF N-TRIMETHYLSILYLPYRROLES AS DIENES IN THE DIELS-ALDER REACTION. SYNTHESIS OF 1,4-DIHYDRONAPHTHALEN-1,4-IMINES

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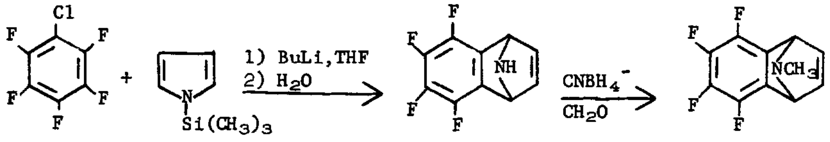
Recent interest in the chemistry of 1,4-dihydronaphthalen-1,4-imines prompts this report of an extremely useful synthetic variation[1] of the classical Diels-Alder approach to this ring system which was first described by Wittig.[2-11] The addition of benzyne to N-methylpyrrole is of limited synthetic utility, however, due to the instability of the product under the reaction conditions.[11,12] Methodology for circumventing this problem by using t-butyl pyrrole-1-carboxylate as the diene has been described by Carpino.[13] Although the N-t-butoxycarbonyl group serves to protect the product from secondary benzyne reactions, an additional carefully controlled acid hydrolysis step is required to remove this protecting group. This communication describes a method for eliminating this operation and thus significantly enhances the overall synthetic utility of the Diels-Alder approach to 1,4-dihydronaphthalen-1,4-imines.

Although the addition of benzyne to N-methylpyrrole leads mainly to a product resulting from the attack of a second benzyne molecule on the basic nitrogen of the initially formed 1,4-dihydronaphthalen-1,4-imine, tetrafluorobenzyne adds smoothly to yield the normal Diels-Alder adduct, 5,6,7,8-tetrafluoro-9-methyl-1,4-dihydronaphthalen-1,4-imine (IV).[14] An interest in the synthesis of the des-methyl analog III, prompted an attempt to add tetrafluorobenzyne to t-butyl pyrrole-1-carboxylate using the Carpino method. Surprisingly, this usually successful procedure failed to yield the desired 1,4-dihydronaphthalen-1,4-imine. This result coupled with a consideration of possible alternative routes to III suggested that a pyrrole with a more inert N-protective group should be employed. The use of N-trimethylsilylpyrrole was particularly attractive since the removal of the protecting group from the product might be expected to be facile. In fact, tetrafluorobenzyne adds smoothly to N-trimethylsilylpyrrole to establish the 1,4-dihydronaphthalen-1,4-imine ring system. Furthermore, simple addition of water to the anhydrous reaction medium serves to remove the protecting group and complete the synthesis of the desired des-methyl compound III.



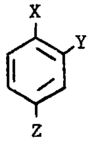
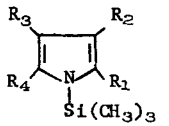
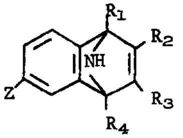
I II III IV

Although the synthesis of 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalen-1,4-imine, the dihydro analog of III, was recently reported by catalytic hydrogenation of 9-benzyl-5,6,7,8-tetrafluoro-1,4-dihydronaphthalen-1,4-imine, this method does not allow the synthesis of III. The approach described here constitutes the first synthesis of III. The structure of III, b.p. 90-92°/3 mm, was confirmed by its nmr spectrum (60 MHz in $CDCl_3$, TMS as internal standard): δ 3.35, assigned to the N-H; δ 5.7, assigned to the bridgehead protons and δ 7.4, assigned to the olefinic protons. Structure III is further supported by its mass spectrum: m/e 215, parent molecular ion; m/e 189, the isoindole resulting from a retro Diels-Alder reaction of III; m/e 162, the loss of HCN from the isoindole. In addition, treatment of III with aqueous formaldehyde and sodium cyanoborohydride as described by Borch[15] provided a 75% yield of the known tertiary amine IV. This reductive alkylation of III by the Borch procedure is of particular interest since a competitive reduction of the olefinic linkage is not observed.[2]

The uniqueness of this application of N-trimethylsilylpyrroles as dienes in the Diels-Alder reaction with benzynes lies in its complete generality. In addition to II, 2,5-disubstituted and 3,4-disubstituted N-trimethylsilylpyrroles have been employed as dienes. The reaction is successful with a broad range of benzynes differing in chemical reactivity, since the N-trimethylsilyl group protects the product from secondary benzyne reactions yet does not impede the chemical reactivity of the pyrrole diene system. Furthermore, it is not necessary to subject the product to acidic conditions since the protecting group is readily removed by addition of water. Thus, even extremely acid sensitive 1,4-dihydronaphthalen-1,4-imines can be prepared by this method. It should be noted that excess N-trimethylsilylpyrrole is not hydrolyzed under these conditions and may be recovered by distillation.

The broad scope of this synthetic method is suggested by the further examples in Table 1. The Diels-Alder addition of benzyne, tetrafluorobenzyne and several monosubstituted benzynes to N-trimethylsilylpyrrole, 3,4-dimethyl-, 3,4-dichloro- and 2,5-dimethyl-N-trimethylsilylpyrrole has been successfully achieved in 30-50% yield.

Table 1

Reaction No.				Method	Yield[18]
1	X=Br,Y=I Z=OCH_3	$R_1=R_2=R_3=R_4=H$	$R_1=R_2=R_3=R_4=H$ Z=OCH_3	B	43
2	X=Cl,Y=Br Z=CF_3	$R_1=R_2=R_3=R_4=H$	$R_1=R_2=R_3=R_4=H$ Z=CF_3	A	39
3	X=Z=F Y=Br	$R_1=R_4=H$ $R_2=R_3=CH_3$	$R_1=R_4=H$ $R_2=R_3=CH_3$ Z=F	A	50
4	X=Br,Y=F Z=H	$R_1=R_4=CH_3$ $R_2=R_3=H$	$R_1=R_4=CH_3$ $R_2=R_3=H$ Z=H	A	33
5	X=Z=F Y=Br	$R_1=R_4=H$ $R_2=R_3=Cl$	$R_1=R_4=H$ $R_2=R_3=Cl$ Z=F	A	40
6	X=Cl,Y=Br Z=CH_3	$R_1=R_2=R_3=R_4=H$	$R_1=R_2=R_3=R_4=H$ Z=CH_3	B	50

In practice, the benzyne was generated *in situ* from the appropriate precursor in an ethereal medium by one of the following two methods:[16] Method A, addition of butyllithium to an *o*-dihalobenzene in ether at -60°C followed by addition of the *N*-trimethylsilylpyrrole; Method B, addition of an *o*-dihalobenzene to a THF solution of the *N*-trimethylsilylpyrrole slurried with magnesium metal at the reflux temperature of the solvent. Method B was the method of choice for generating benzynes containing a methoxy or methyl substituent while Method A gave the best results with benzynes having a halogen or trifluoromethyl substituent. Tetrafluorobenzyne was generated by addition of butyllithium to chloropentafluorobenzene.

The preparation of the *N*-trimethylsilyl derivatives of pyrrole and the 3,4-disubstituted pyrroles was achieved by the published procedure in which the pyrrole is heated under reflux for several hours with excess 1,1,1,2,2,2-hexamethyldisilazane.[17] The more hindered 2,5-dimethylpyrrole required the use of a two-step procedure in which the potassium derivative was prepared initially and subsequently treated with trimethylsilylchloride.

The structures of the 1,4-dihydronaphthalen-1,4-imines indicated in Table 1 were confirmed by proton nmr spectroscopy. These compounds are sensitive to mineral acids and prolonged exposure to light and moist air; however, they may be stored conveniently as stable hydrogen fumarates that are obtained by treatment with fumaric acid in isopropanol. In addition, these secondary amines are readily converted to the corresponding *N*-methyl analogs in 50-75% yield by the Borch procedure.[15]

The simplicity of this synthetic method is illustrated by the following example:

1. 6-Methoxy-1,4-dihydronaphthalen-1,4-imine. Method B.

A mixture of 2-iodo-4-methoxybromobenzene (12.6 g, .04 mol), magnesium (1.0 g, .04 mol) and N-trimethylsilylpyrrole (8.3 g, .06 mol) in THF (100 ml) was stirred and heated under reflux under N_2 for 3 hr., cooled, and poured into ice water. The product was isolated by ether extraction and purified by distillation, b.p. 85-88° (5 mm). The distillate (3.0 g) was added to a warm solution of fumaric acid in isopropanol to obtain on cooling a hydrogen fumarate, m.p. 170-172°. The yield was 4.8 g (42%).

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