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A SUBSTITUTED BENZENE RING SYNTHESIS

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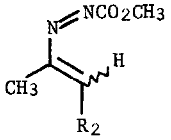
N-Aminopyrroles are used in a new, versatile and high yield substituted benzene ring synthesis

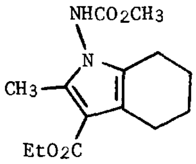
The usual strategy for synthesis of a molecule containing an aromatic ring is to build the molecule around a readily available benzene precursor. This approach often results in problems associated with the introduction of substituents at specific positions on the benzene ring. The alternative approach, a benzene ring construction, may offer the advantage of ring substitution control and in fact many methods based on the sequence bridged diene → Diels-Alder adduct → benzene ring have been reported.[1a]

While a variety of diene systems have been employed in benzene ring construction, the utilization of pyrroles has never been reported.[1b] In this regard, it is generally recognized that simple pyrroles are prone to undergo substitution with electron deficient olefins and acetylenes rather than Diels-Alder addition.[2] Herein we report that N-aminopyrroles undergo efficient Diels-Alder reaction with electron deficient acetylenes and, coupled with the azoalkene based N-aminopyrrole synthesis, this observation provides a remarkably simple method for substituted benzene ring construction.

Reaction of N-carbomethoxyaminopyrrole 2 with excess dimethyl acetylenedicarboxylate in refluxing toluene (48 h) gives the tetralin 3a in 55% isolated yield. In contrast to 2, pyrroles 4a and 4b (*vide infra*) give uncharacterized product mixtures and no substituted benzene derivatives. On the other hand, pyrroles 4c and 4d react with DMAD to give 5a and 5b respectively in good yield. Thus, N-carbomethoxyaminopyrrole addition to DMAD is possible when one electron withdrawing group is present at C(3), but not when two such groups are present at C(3) and C(4).



1a, $R_2 = CO_2Et$
b, $R_2 = C_6H_5$



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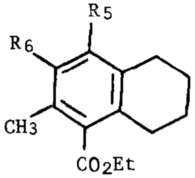
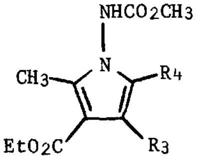
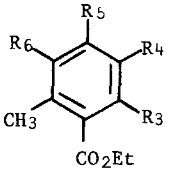


3a, $R_5 = R_6 = CO_2CH_3$
b, $R_5 = H$; $R_6 = CO_2Et$
c, $R_5 = CO_2Et$; $R_6 = H$



4a, $R_3 = CO_2Et$; $R_4 = CH_3$
b, $R_3 = COCH_3$; $R_4 = CH_3$
c, $R_3 = CH_3$; $R_4 = C_2H_5$
d, $R_3 = C_2H_5$; $R_4 = CH_3$

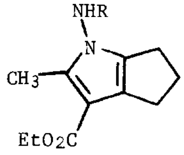


5a, $R_3 = CH_3$; $R_4 = C_2H_5$; $R_5 = R_6 = CO_2CH_3$
b, $R_3 = C_2H_5$; $R_4 = CH_3$; $R_5 = R_6 = CO_2CH_3$
c, $R_3 = C_2H_5$; $R_4 = CH_3$; $R_5 = H$; $R_6 = CO_2Et$
d, $R_3 = C_2H_5$; $R_4 = CH_3$; $R_5 = CO_2Et$; $R_6 = H$

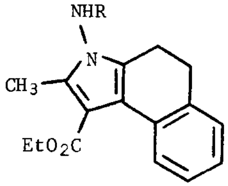
Pyrrole 4c is prepared from azoalkene 1a and the morpholine enamine of 3-pentanone[3] (86%, mp 109-110°C), and 4b from 1a and 2,4-pentanedione (89%, mp 85-86°C); reduction of 4b with excess zinc in refluxing acetic acid gives 4d (72%). Isomeric pyrroles (*e.g.*, 4c and 4d), and hence benzene derivatives 5a and 5b are, therefore, readily available by these complementary methods.

N-carbomethoxyaminopyrroles also react with ethyl propiolate, albeit with little regiochemical control; *e.g.*, 2 → 3b (60) + 3c (40) and 4d → 5c (85) + 5d (15). The major product in both of these examples is that resulting in para orientation between the C(4) alkyl substituent on the pyrrole (diene component) and the carboethoxy substituent on the acetylene (dienophile).

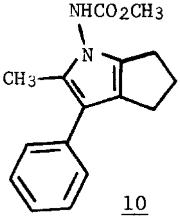
While yields for many reactions of N-carbomethoxyaminopyrroles with acetylenes are good (50-60%) we were concerned with the rather vigorous conditions required (refluxing toluene). With sensitive systems these reaction conditions result in decreased yields (e.g., 6a → 7; 13% yield). However, 6b (prepared by brief treatment of 6a with NaCN in warm hexamethylphosphoramide)[4] reacts with DMAD (3 equiv) in $CHCl_3$ solution at room temperature to give 7 in 50% isolated yield. The enhanced reactivity of N-aminopyrroles seems general and is of clear synthetic value. Thus, whereas 8a (obtained from the pyrrolidine enamine of β-tetralone; mp 155-157°C, 72%) reacts with DMAD to give the 9,10-dihydrophenanthrene 9 in 50% yield, the reaction of 8b gives 9 in >90% isolated yield.



6a, R = CO_2CH_3
b, R = H



8a, R = CO_2CH_3
b, R = H



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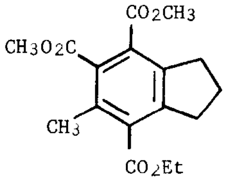

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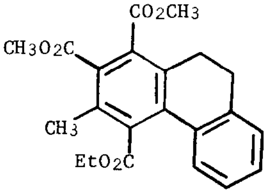

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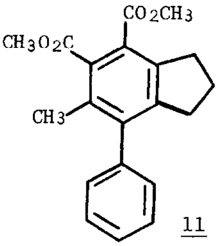

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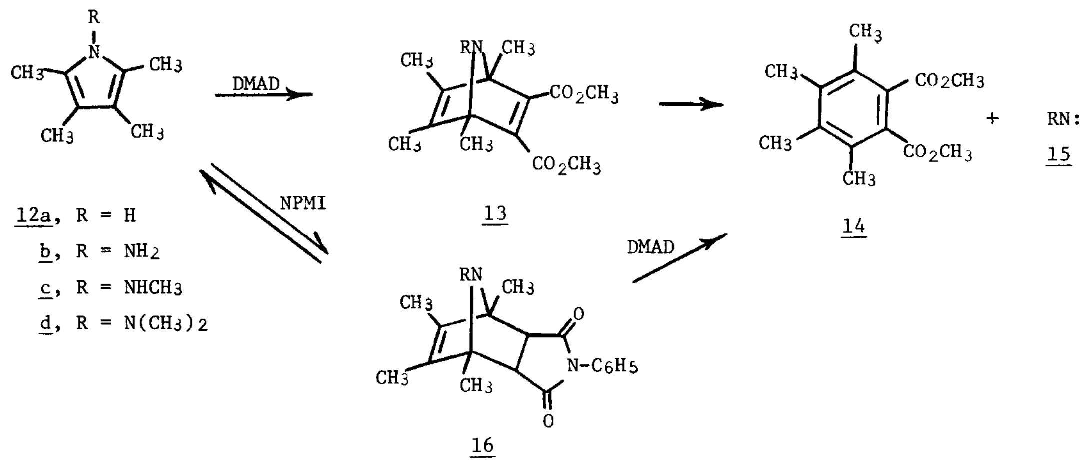
The reaction of pyrrole 10 with DMAD gives biaryl 11 in excellent overall yield from azoalkene 1b. The preparation of 11 is interesting because it represents potentially useful alternate methodology to the Ullmann type biaryl synthesis.[5]

We have not been able to detect the formation of benzene derivative 14 in reactions of the N-unsubstituted pyrrole 12a with DMAD. On the other hand 12b-12d all react with DMAD to give 13 (^1H NMR experiment) and eventually 14. It is noteworthy that the observed rate of addition increases in the order 12b > 12c > 12d, whereas adduct decomposition to 14 increases in the order 13d > 13c > 13b. For example, in $CDCl_3$ solution at 30°C, 12c (0.3 M) is 70% consumed in 5 min and within 45 min, conversion to 14 is complete.



An NMR spectrum obtained immediately after mixing 12c with *N*-phenylmaleimide (NPMI, 1 equiv) suggests the presence of adduct 16c. The spectrum does not change with time; however, resonances assigned to 16c increase on continued addition of NPMI (max 10 equiv, ∿ 90% 16c present). Adduct 16c is not stable to silica gel chromatography and when DMAD is added to the mixture of 12c and NPMI, 14 is formed in 70% isolated yield.

From all these data, we conclude that Diels-Alder addition to pyrroles is reversible[2] and the heteroatom bridge in the resulting adduct is extruded only when a benzene ring will result. Furthermore, we suggest that formation of 14 from 13b-13d occurs by extrusion of the relatively stable nitrenes 15b-15d.[6] Experiments designed to further examine the synthetic potential of this new benzene ring synthesis and test certain mechanistic questions are in progress and will be reported in detail.

Acknowledgement

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