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STRONG BASE INDUCED INTRAMOLECULAR CYCLOADDITION OF HOMOPHTHALIC ANHYDRIDES LEADING TO POLYCYCLIC PERI-HYDROXY AROMATIC COMPOUNDS

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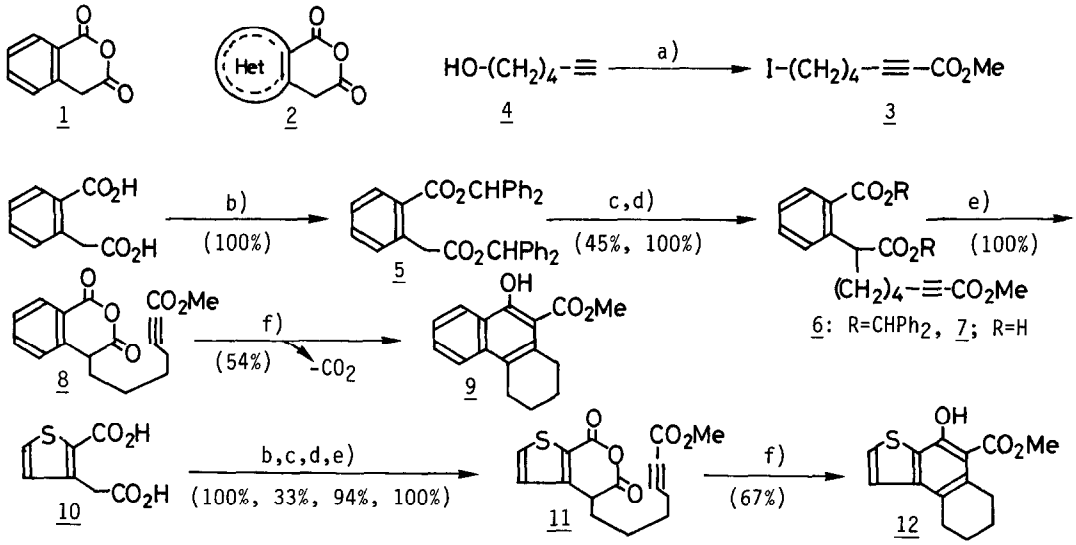
Summary; A strong base-induced intramolecular cycloaddition reaction homophthalic anhydride has been examined as a method for preparing polycyclic peri-hydroxy aromatic compounds.

Homophthalic anhydrides (1) and their hetero analogues (2) have been used for the construction of various types of polycyclic aromatic and heteroaromatic compounds leading to alkaloids, antibiotics, and pharmacologically important compounds.[1,2] Recently we reported that homophthalic anhydrides undergo regiospecific cycloaddition to electron-poor carbon-carbon multiple bonds in thermal conditions[3] and in the presence of a strong base such as lithium diisopropyl amide (LDA) or sodium hydride (NaH).[4] The latter base-induced cycloaddition reaction was successfully applied to a facile regiocontrolled synthesis of biologically important peri-hydroxy aromatic compounds such as anthracyclines,[5] heteroanthracyclines,[6] and SS-228R.[7] Although the intermolecular version of the cycloaddition has received considerable attention, no intramolecular type of cycloaddition has ever been reported. We describe here the first intramolecular cycloaddition of homophthalic anhydrides and related anhydride having an electron-poor acetylene bond leading to non-linear tricyclic aromatic compounds in considerable yields.

The iodide (3) was prepared from the known alcohol (4) in 88% overall yield. The diester (5), obtained from homophthalic acid and diphenyldiazomethane was alkylated with 3 to give the 2-alkylated phenylacetate (6). Selective deprotection of the diphenylmethyl group of 6 without demethylation of the terminal ester with boron trifluoride etherate[8] gave the diacid (7), which was dehydrated with (trimethylsilyl)ethoxyacetylene[9] to give the anhydride (8). Although 8 refused to cyclize under thermal conditions, strong base treatment of it caused a smooth intramolecular cycloaddition reaction followed by spontaneous extrusion of carbon dioxide under the conditions giving tetrahydrophenanthrene (9).

The generality of the present intramolecular cycloaddition reaction was ascertained in the thiophene analogue of 8. The anhydride (11) was prepared from (2-carboxythiophen-3-yl)acetic acid (10)[10] by a series of procedures similar to those described for the preparation of 8 from homophthalic acid.

(11) was treated with NaH in anh. THF at r.t. for 2h to give the cycloaddition product (12) in 21% overall yield from 10.



a) (i) 3,4-dihydro-2H-pyran/cat. p-TsOH, r.t. 3h (97%), (ii) n-BuLi/$ClCO_2Me$/THF, -78°C, 30min (96%), (iii) p-TsOH/MeOH, r.t. 1day (100%), (iv) MsCl/Et_3N/CCl_4, r.t. 9h (100%), (v) NaI/acetone, r.t. 4day (95%), b) Ph_2CN_2/CH_2Cl_2, r.t. 2.5h. c) (i) LDA/THF, -78°C, (ii) 3/1%HMPA-THF, -78°C, r.t. 2h. d) $BF_3.Et_2O$/AcOH, 0→r.t. 1h. e) TMS-≡-OEt/CH_2Cl_2, r.t. 3-5h. f) 1.3-3eq NaH/anh. THF, r.t. 1-2h.

The above described methodology opens an elegant and straightforward approach to non-linearly condensed polycyclic aromatic compounds such as resistomycin,[11] heliomycin,[12] urdamycin,[13] and actinoplanone.[14]

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