Heterocyclic Letters
Vol. 15| No.2|269-272|Feb-April|2025
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF 13-METHYLDIBENZOFLOURENE DERIVATIVES AS ANTICANCER AGENTS

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Abstract:
Acid-induced cyclodehydration and aromatization are investigated for the synthesis of a few polyaromatic compounds. These molecules are tested *in vitro* against a number of human cancer cell lines and anticancer 13-methyldibenzoflourene derivatives have been identified.

Keywords:
Cyclodehydration, Aromatization, 13-Methyldibenzoflourenes, Cancer, Biological Evaluation

Introduction:

Synthesis of polyaromatic compounds is conducted by many researchers. Most of the synthesis involves multiple steps.[1] The anticancer properties of polyaromatic compounds depends on their intercalating activity with DNA or interaction with DNA associated enzymes.[2] During our studies on polyaromatic molecules as anticancer agents, we have identified substituted chrysenes as anticancer agents.[3] We describe here an acid-induced dehydration-aromatization route toward the synthesis of methyldibenzoflourene. A few derivatives are prepared using dibenzoflourene. The anticancer activities of these types of dibenzoflourenes are also studied *in vitro* and the results are reported below.

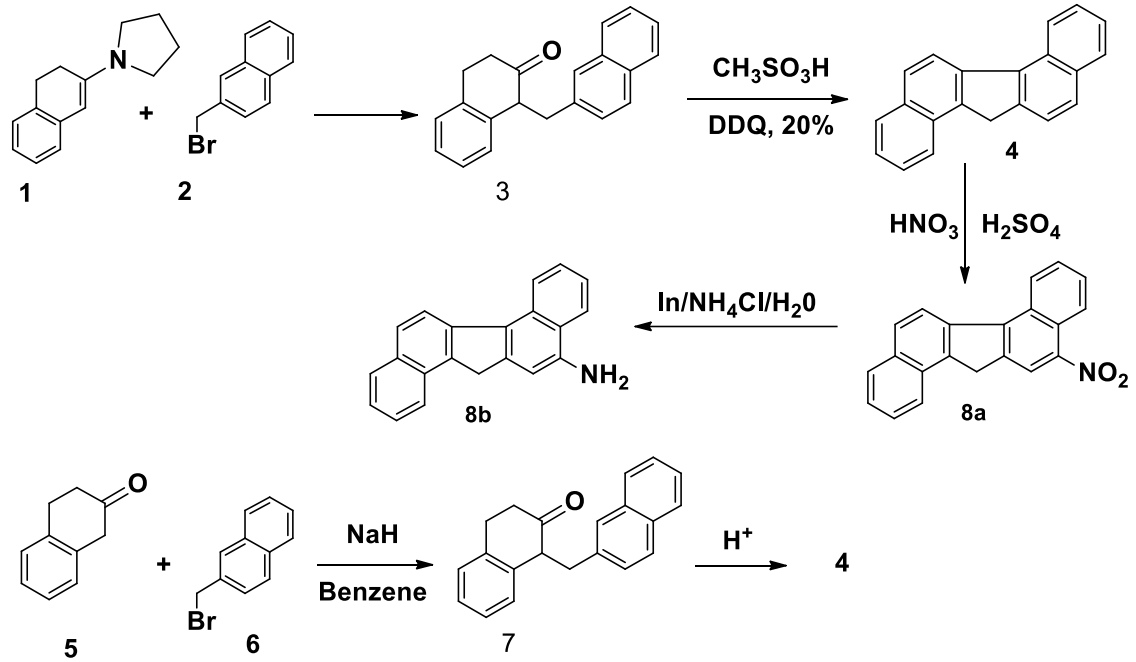
Results and Discussions:

Polycyclic aromatic compounds have demonstrated anticancer activity through DNA intercalation and biding properties.[4]We hypothesize that a benzylic methylene and methine group in the polyaromatic compounds may become useful in the studies of the anticancer activities of these types of compounds. Because of diverse reactivity, these groups are able to form cation, anion, and radical under cellular environment. Toward the goal, synthesis and antitumor activities of angular dibenzoflourene [a,g] polycyclic system with a bridged methyl

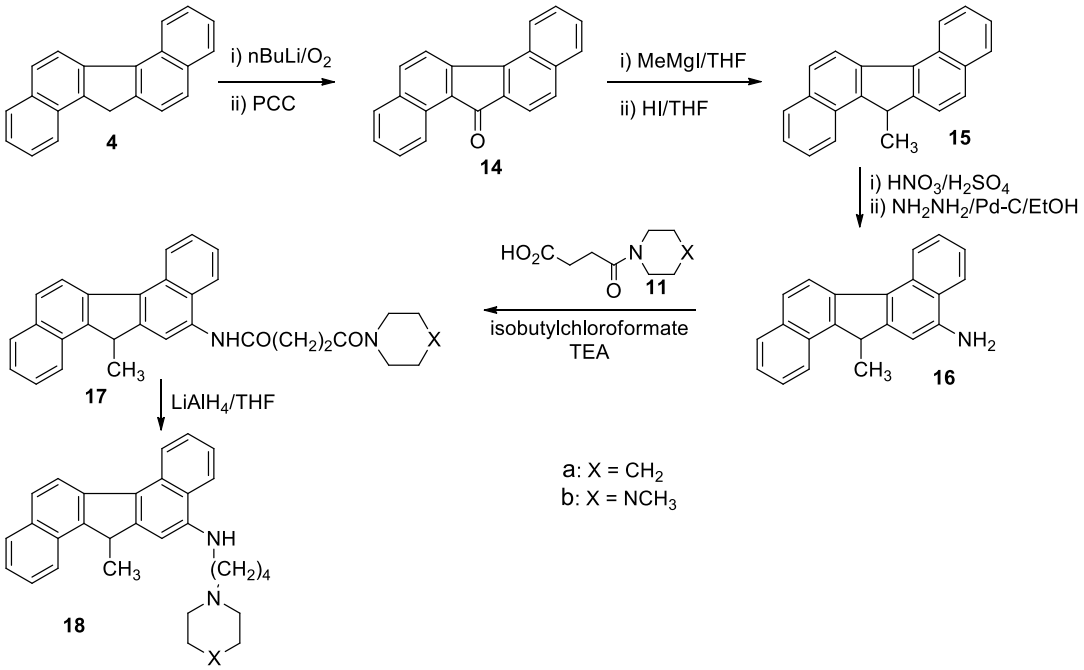
group is performed. The structure-activity relationships of the new compounds as anticancer agents are also reported here.

Dibenzo[a,g]flourene (**4**) was prepared first. The ketone **3** was synthesized *via* alkylation of the enamine **1** with the bromide **2.** Cyclodehydration-aromatization of the ketone **3** afforded the hydrocarbon **4** (**Scheme 1**). Alternatively, the compound **4** was also prepared using enolate chemistry. Reaction of ketone **5** with bromide **6** in the presence of a strong base afforded the alkylated ketone **7** which was cyclized by cyclodehydration-aromatization method to **4**. The hydrocarbon **4** was nitrated successfully and the nitro derivative **8a** was reduced to amine **8b**[5].

Scheme 1



The keto compound **14** prepared by an oxidation experiment on the treatment with methylmagnesium iodide and dehydration in the presence of acid afforded the methylated dibenzoflourene **15.** Nitration, reduction of the nitro group and coupling reaction afforded the amide **17** in excellent yield. The amide was successfully reduced by lithium aluminum hydride to the amine **18 (Scheme 2)**.



The antitumor activity of these newly synthesized dibenzoflourene derivatives **17** and **18** were tested and a comparison with respect to cisplatin was performed. The diamides with N-methyl piperazine **17b** was more potent than the diamides with piperidine **17a,** but it was less active than cisplatin. However, the two diamines **18a** and **18b** are potent irrespective of the terminal groups. Interestingly, the activity of these two compounds (**18a** and **18b**) is similar to cisplatin. The amino products exhibited IC_{50} 1 to 4.6 (μM) against B16, BRO, HL-60, L-1210, MCF-7, OVCAR-3, P-388 and PC-3 cancer cell lines by MTT assay (72 hr continuous exposure). The final concentration of solvent was <0.625%, which was not toxic to the cells. All dilutions were made in RPMI 1640 with 10% FBS. The cytotoxicity data are based on at least 3 separate experiments with deviations within 0.2 μM.

Conclusions:

Synthesis of new polyaromatic methyldibenzoflourenes is achieved through a convergent route. Remarkably, these molecules have demonstrated anticancer activity against a number cancer cell lines. These crucial studies offer excellent possibilities to expand research on polyaromatic compounds to demonstrate their effective synthesis and selective anticancer activities *in vitro* and *in vivo*.

Acknowledgments:

The anti-tumor activity was assayed by Dr. Robert Newman in the Pharmacology and Analytical Core Laboratory (2P30CA16672-23).

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Received on March 24, 2025.