

1H- indole-2-carboxylate

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Abstract:-

A number of indole derivatives were prepared by reaction of a series of available aromatic aldehyde with ethyl azido acetate followed by thermolysis of the resulted vinyl nitrene intermediates. These derivatives can be used as precursor for the antitumour CC-1065.

Introduction:-

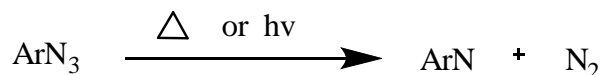
There have been a number of reports the literature discussed the synthesis of indole derivatives. One of these procedure are mentioned by Farlow et. al.⁽¹⁾ Also oxidntlyl derivatives were prepared according to procedure described by Hinman et. al.⁽²⁾

The indolyl derivatives including azido group in the 5-position were also prepared by treating of Meldrum's acid with 1 equiv. of NBS in 95% t-butyl alcohol according to a method described by Labroo et al.⁽³⁾

Studies have been carried are the oxindole derivatives and they found that the inhibitory activates of these derivatives were better than indoly.⁽⁴⁾

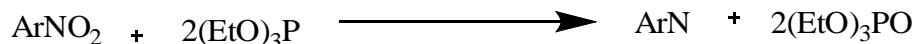
The biological study on different β -substitution tryptophanes and tryptamines were required , thus Yonemitsu reaction⁽⁵⁾ involving indole, aldehyde and Meldrum's acid were studied. The condensation which involves the three components were converted to β -substitution tryptophanes by ring opening of the dioxane moiety with alcohol , followed by acylazide formation and curtius rearrangement as key step.⁽⁶⁾

The most general and widely used method to prepare aryl mitrene is thermolysis or photolysis of aryl azides which readily loss two of the three nitrogen as N_2 . For thermolysis, the temperature required for simple phenyl azides is in the range 130-180 °C. , although for temperature can be used if one is willing to tolerate the resulting slowness. Aryl azides are nearly thermolysed in dilute solution in a solvent chosen for its boiling point and inertness. Hydrocarbons and their halogenated derivatives are commonly used. The advantage of using a solvent is to have a smooth and more safer reaction. Dilution may also minimize the formation of polymericraterials .



Photolysis is generally effected by near UV radiation even sunlight can be used. Also solvent is important for the same reasons as apply to thermolysis. The solvent should be transparent to UV light, and aromatic solvents are therefore commonly avoided unless there is specific reason to use them.

Tetrahydrofuran THF is a widely used solvent for photolysis.⁽⁷⁾ Deoxygenation of nitro and nitroso compounds is the next most widely used method for generating aryl nitrenes⁽⁸⁾.



In general the same sort of products are formed as from aryl azides⁽⁹⁾. Brooke et. al.⁽¹⁰⁾ reported differences in product ratios when coppering thermolysis of some o-azidobiphenyl.⁽¹¹⁾

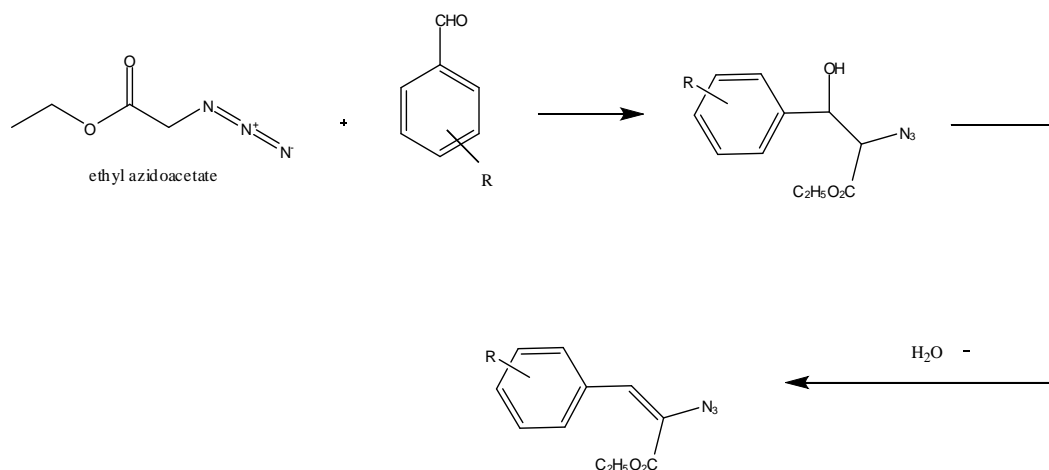
Experimental

Preparation of ethyl azidoacetate

Ethyl chloroacetate (5g, 5 mol) and sodium azide (4g, 6 mol) was stirred in ethanol and water (150 ml) and the reaction mixture was heated under reflux for 5h. On cooling, water was added and then the solution was extracted by separated funnel. The organic layer was serrated and the aqueous layer extracted with dichloromethane. The combined, dried (MgSO_4), filtered and evaporated under reduced pressure to give 3g (65%) of colorless liquid which was used with out further purification.

Condensation of ethyl azidoacetate with 5-bromo salicylaldehyde

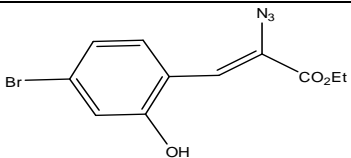
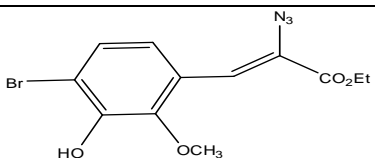
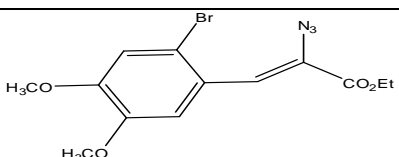
Sodium methoxide (1g, 6mol) was added during 10min to a stirred and cooled solution of 5-bromo salicylaldehyde (5g, 2mol) and ethyl azidoacetate (5g, 1mol) in methanol (15 ml). The reaction mixture was stirred at room temp. for 2h and the solvent was evaporated under reduced pressure.



The residue was neutralized with dilute HCl and the mixture was extracted with ethyl acetate. The combined organic extracts were dried, filtered, and evaporated under reduced pressure to give vinyl azide as crude product.

Recrystallization from ethanol gave 3g (55%) of pure product. The other azide derivatives were prepared under similar procedure and the results are obtained in table (1).

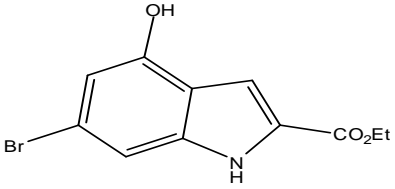
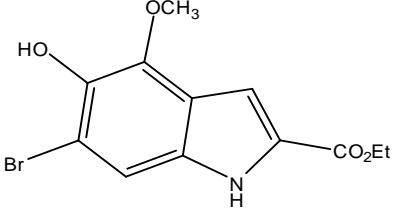
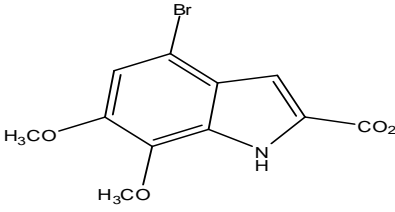
Table(1) : Show the result of the condensation of ethyl azidoacetate with aromatic aldehyde

Comp.	M.P. °C	Yield%	IR (nujol) cm ⁻¹	¹ HNMR(CDCl ₃)
	102-105	55	vN ₃ 2100 v C=O 1710 v OH 3300-3500	δ 6.8-8 (3H,m,ArH) δ 8.2(1H,s, HC=C-CO ₂ C ₂ H ₅) δ3.9(2H,tetra,OCH ₂) δ1.3(3H,t,CH ₃)
	120-122	80	vN ₃ 2110 v C=O 1710 v OH 3300-3500	δ 6.8-8 (3H,m,ArH) δ 8.2(1H,s, HC=C-CO ₂ C ₂ H ₅) δ3.9(2H,tetra,OCH ₂) δ1.3(3H,t,CH ₃) δ3.2(3H,s,OCH ₃)
	141-144	65	vN ₃ 2110 v C=O 1710	δ 6.8-8 (3H,m,ArH) δ 8.2(1H,s, HC=C-CO ₂ C ₂ H ₅) δ3.9(2H,tetra,OCH ₂) δ1.3(3H,t,CH ₃) δ3.2(6H,s,OCH ₃)

Thermolysis of vinyl azide

The prepared vinyl azides was dissolved in xylene and the solution heated under reflux for 2-5h , after which the solvent was evaporated under reduced pressure to give a yellow oil. Column chromatography using CH₃Cl as a solvent gave the corresponding indole derivative as shown on table(2).

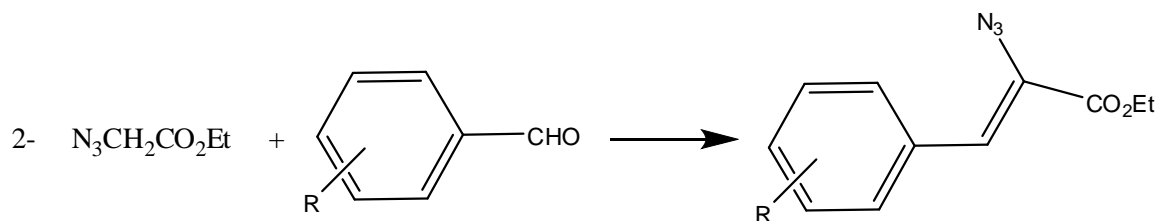
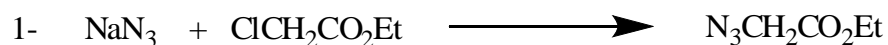
Table (2): Show the results of thermolysis of vinyl azido compounds

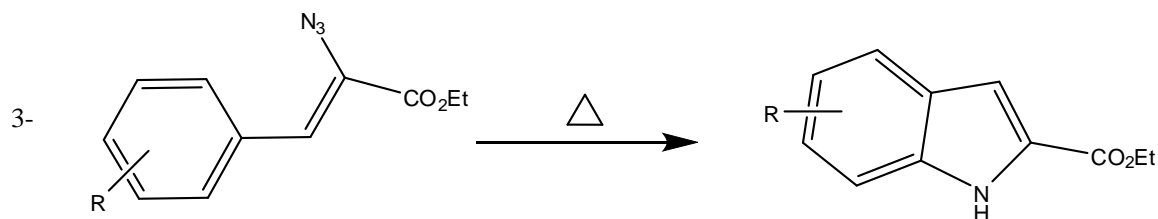
Comp.	M.P .°C	Yield %	IR (nujol) cm ⁻¹	¹ HNMR(CDCl ₃)
	135- 138	65	v NH 3320 v C=O 1700	δ3.8(2H,tetra,OCH ₂) δ1.3(3H,t,CH ₃) δ 7.2(3H,m,ArH, HC=C-CO ₂ C ₂ H ₅)
	155- 158	72	v NH 3320 v C=O 1700	δ3.8(2H,tetra,OCH ₂) δ1.3(3H,t,CH ₃) δ 7.2(3H,m,ArH, HC=C-CO ₂ C ₂ H ₅)
	170- 173	83	v NH 3320 v C=O 1700	δ3.8(2H,tetra,OCH ₂) δ1.3(3H,t,CH ₃) δ 7.2(3H,m,ArH, HC=C-CO ₂ C ₂ H ₅)

Result and Discussion:-

The route which was devised for the synthesis of ethyl-2-azido-1H-indole-2-carboxylate is shown in scheme (1).

Scheme(1)





In the first step sodium azide was reacted with ethyl chloroacetate in reaction to form ethyl azidoacetate. The second step involves abstraction of the acidic hydrogen in ethyl azidoacetate by the base to form a carbanion ion as follows.



Then the carbanion will react with any aromatic aldehyde to form the vinyl azide derivative after loss of a molecule of H_2O , as shown in the scheme.

In the third step is the thermolysis of the resulting vinyl azide to an indole derivative. This step involves loss of two of the three nitrogens as N_2 to generate a nitrene intermediate which undergoes cyclization to an indole derivative under the reaction conditions.

Finally, these indole derivatives can be used as precursors for the antitumor molecule CC-1065, which is one of the most cytotoxic antitumor agents known.

References:-

1. P.S. Farlow ; M.E. Flaugh ; M.E. Horvath and S.D. Lawgnino; *Org. Prep. Procint.* ; 13, 39, (1981).
2. R. L. Hinman ; C. P. J. Bauman ; *J. Org. Chem.* , 29, 120,(1964).
3. R. B. Labroo; L. A. Cohen ; *J. Org. Chem.*; 55 ,4901,(1990).
4. I.O. Donks et al ; *J. Med. Chem.* ; 33, (1998).
5. O. Yonemitsu ; Y. Oikawa ; H. Hirasawa ; *Tetrahedron lett.* ; 20 , 1759 – 1762 , (1978).
6. J. Sapi ; “Multicomponent Approach Toward Polycyclic Indole Derivatives of Biological Interest” ; *Reims Cedex* , PL-8.
7. I. Ugi ; *Tetrahedron Lett.*; 1, 1901,(1963).
8. J. H. Boyer ; 'nitrenes' , Wiley , New York , 163-184,(1970).
9. J. I. G. Cadogan ; *Rev. Chem. Soc.* ; 22,222 (1964).
10. P. K. Brooke ;R. B. Herbert and F. G. Holliman , *Tetrahedron lett.* ;761,(1973).
11. Vinylazides in Heterocyclic Synthesis Commum ; 1775, (1985).
12. L. G. Haamka ; A. Dietz and D. G. Martion, *J. antibiot.* ; 31 , 1211,(1978).
13. C. G. Child ester ; W. C. Kruegen and D. J. Dunchamp; *J. Amer. Chem. Soc.* , 103, 7629,(1981).

الاندول كاربوكسيلا٢H1- تحضير وتشخيص عدد من مشتقات ائيل-2- ازايڊو-

ناجي موسى علي
كلية الصيدلة/جامعة الكوفة

الخلاصة :-

لقد تم تحضير وتشخيص عدد من مشتقات ازايڊو الاندول كاربوكسيلا٢ من خلال تفاعل الالديهائيات الاروماتية مع اسيتات ائيل-2- ازايڊو ومن ثم السحق الحراري لنواتج النايترين الوسطي. ان هذه المشتقات يمكن الاستفادة منها من استخدامها كمواد أولية ورئيسية للجزيئة المعروفة بـ CC-1065 التي تعمل كمضادات للأورام الخبيثة.