Pakistan J. Sci. Ind. Res., Vol. 27, No. 2, April 1984

BEHAVIOUR OF 3 [2′–(3′, 1′)-BENZOXAZIN-4′-ONYL] COUMARIN TOWARDS CARBON AND NITROGEN NUCLEOPHILES (CONTRASTING THE REACTIVITY OF α-PYRONE AND OXAZINONE RINGS)

M. Elkady, M. El-Hashash,* R.M. Saleh,* and A.M. El-Gendy*

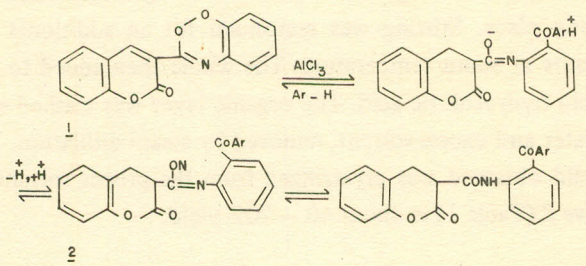
Chemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt

(Received January 2, 1983)

Alkylation of 3 [2′-(3′, 1′)-benzoxazin-4-only] coumarin *1* under Friedel Craft's condition gave 3(2′-aroylaniline) carbonyl-3, 4-dihydrocoumarin *2*. Acid hydrolysis of *2* yielded 3,4-dihydrocoumarin-3-carboxylic acid *3*a; which on reacting its acid chloride *3*b with amines gave the corresponding amide *4*. *1* also reacted with hydroxylamine hydrochloride or semicarbazide hydrochloride to yield the corresponding isoxazolidine *5* and triazole derivative respectively. Michael reaction of *1* with camphor and methyl isopropyl ketone have been utilized in the synthesis of *7* and *9*.

INTRODUCTION

In continuation of the previous study [1-4], in the present investigation, the alkylation of 3[2′(3′, 1′)-benzoxazin-4-onyl] coumarin (*1*) under Friedel Craft's condition, with aromatic compounds namely *p*-xylene, *o*-xylene, *m*-bromotoluene, *p*-bromotoluene and bromobenzene yielded (3-(2′-aroyl-anilino) carbonyl-3,4-dihydrocoumarins 2a-e. The formation of *2* a-e can be readily interpreted from the fact that 2-cyclohexyl-3, 1, 4-benzoxazone reacts with aluminium chloride in toluene to give 2-cyclohexoylamido-p-methylbenzophenone [5] and the 3-carbethoxycoumarins react with aluminium chloride in aromatic hydrocarbons to give one compound identified as 3-carbethoxy-3, 4-dihydrocoumarins (*3c*) [6]. The yielding of *2* a-e takes place according to the following mechanism.



1

2

* Faculty of Engineering, Port Said, Egypt.
* Faculty of Science, Zagazig University, Egypt.

The structures of *2*a-e were established from the following assignments:

i) Correct analytical values.

ii) The infrared spectra of *2* exhibited bands attributable to the carbonyl of saturated δ-lactone (1770 – 1740), γCO of ketone (1690 – 1680), δCO of amide (1660 – 1650) and γNH group at (3210 – 3190).

iii) The ^{1}–HNMR spectrum of *2e* in $CDCl_3$ showed triplet at 3.3 integrating for *lH* of H-3. Doublet at 4.3 integrating for *2H* of H-4 and multiplet at 6.4 – 7.8 integrating *12H* of aromatic.

iv) Acid hydrolysis of 2 gave 3, 4-dihydrocoumarin-3-carboxylic acid *3a*. The structure of 3a was proved by its infrared spectrum which showed a band attributable to γCO of saturated δ-lactone (1750), γCO of acid (1700) and γOH (3250).

Also the ethereal layer of the 3, 4-dihydro-3-carbonyl chloride *3b* reacted with amines namely aniline, P-toluidine, α-naphthylamine and/or phenylhydrazine yielding 3-(N-aryl carbamide) -3, 4-dihydrocoumarins (*4a d*). Furthermore *4* can be obtained by condensation of *3C* with the corresponding amines. The structural assignments of *4* were based on infrared spectra which showed absorption bands in the region 1750 – 1730 (CO of saturated δ-lactone), 1690 – 1660 (γCO of amide) and 3280 – 3140 (γNH).

On the other hand base catalysed addition reaction of *1* with hydroxylamine hydrochloride or semicarbazide hydrochloride in boiling pyridine yielded 3, 4-dihyrocou-

marinyl (3', 4' – d) quinazolinyl (2', 3'-b) – isoxazolidine (*5*) and the triazole derivative *6* respectively.

The formation of *5* and *6* can be readily interpreted according to the following mechanism : Nucleophilic attack by the amino group of hydroxylamine or semicarbazide upon carbon of carbonyl group in benzoxazine nucleus took place leading to the opening of the ring followed by cyclization, condensation and addition of the active hydrogen in –OH or –NH – to the olefinic double bond C_3–C_4 in coumarin ring gave the corresponding compound *5* or *6*. This method of base catalysed addition of the active hydrogen in –OH – to C_3–C_4 double bond in coumarin may provide a useful tool for further investigation of this problem. The details of this research will be reported later.

The assigned structure for the products *5* or *6* are inferred from their infrared spectra. The infrared spectrum of *5* shows bands at 1755 attributable to γCO of saturated γ-lactone, at 1680 and 1660 attributable to γCO and γC=N and the absence of any bands characteristic to γNH or γOH.

The ^{1}HNMR spectrum of *5* in $CDCl_3$ showed doublet at 4,1 for *lH* of H.3, doublet at 3.8 *lH* of H-4 and multiplet at 7.2 – 7.9 for *8H* aromatic. Also the infrared spectrum of 6 was consistent with the proposed structure which exhibits strong bands at 1750 (γCO of saturated δ-lactone), 1680 (γCO of amide), 1630 (γC=N) and the absence of any bands characteristic for γOH and γNH. The ^{1}HNMR spectrum of *6* in CD_3COCD_3 showed doublet at 3.9 for *lH* of H-4 and doublet at 3.6 for *lH* of H-3 and multiplet at 6.8 – 7.6 for *8H* of aromatic.

Recently, Sammour [7, 8] *et al.* found that the active methylene compounds underwent Michael addition to the olefinic C_3 – C_4 in coumarins to give pyranobenzopyran-(di or) triones and benzopyranpyridones. Also El-hashash [2, 3] reported that 2-substituted benzoxazones react with ethylacetoacetate, ethylcyanoacetate or diethylmalonate to give the N-substituted anthraniloylacetate. As a point of interest the present work investigated behaviour of *1* toward active methylene compound under Michael conditions. The reaction of *1* with camphor in the presence of sodium ethoxide at 170° yielded 3 (2'-Camphoryl phenyl) carbamido-4-camphoryl-3, 4-dihydrocoumarin *7*. This result can be explained by the addition of the active methylene in camphor to α-pyrone and opening of the oxazinone ring to give 7. The infrared spectrum of *7* shows CO of saturated γ-lactone (1740), γCO of ketone (1680), γCO of amide (1660) and NH (3190). The ^{1}HNMR spectrum of *7* in $CDCl_3$ showed multiplet at 0.9 – 1.6 for *3lH* of camphoryl, doublet at 3.4 for *lH* of H4, doublet at 3.8 for *lH* of H-3 and multiplet at 7.0 – 7.7 for *8H* of aromatic.

Compound *7* undergoes ring closure by acetic anhydride to give 2, 3-Camphor-l-ene-6 [2'-(camphoryl)-benzoyl] iminopyran (3,4 – c) benzopyran-5-one (*8*). The infrared spectrum of 8 shows a broad band centred at 1750 (γCO of saturated δ-lactone), 1620 (γC=N and the absence of any bands characteristic for γOH and γNH.

On the other hand *1* reacts with methyl isopropyl ketone at 170° in presence of sodium ethoxide yielding 1-isopropyl-1, 2-dihydro-6 [2'-(dimethyl acetonyl) benzoyl] iminopyrano- (3,4c) (1) benzopyran-5-one (9). The structure of 9 was supported by infrared spectrum which showed strong bands characteristic to γCO of δ-lactone (1750), γCO of B-diketone (1700) and γC=N (1640). The ^{1}HNMR spectrum of 9 in $CDCl_3$ showed quartet at 1.2 – 1.4 for *12H* of CO-CH $(CH_3)_2$, $-CH(CH_3)_2$, heptet at 2.3 for *lH CH* $(CH_3)_2$, multiplet at 3.5 for *3H* CH_2 *COCH*, 3.7 for doublet *lH* of H-4, 4.1 for douplet *lH* of H-3 and 5.2 singlet *lH* of olefinic and multiplet at 6.8-7.6 *8H* of aromatic.

EXPERIMENTAL

Melting points reported are uncorrected, IR spectra in K Br wafer technique were taken on Unicam SP 1200 Spectrophotometer. ^{1}HNMR were recorded on a Varian (S – 60 T) instrument using TMS as internal standard (chemical shifts in δ-scale).

Friedel-Crafts Alkylation of 1 : Formation of 2. To a solution of *1* (2.9 g, 0.01 mol) in aromatic hydrocarbon namely *p*-xylene, *m*-bromotoluene, *p*-brometoluene and/or bromobenzene (50 ml) Aluminium chloride (0.04 mol) was added. A vigorous evolution of hydrogen chloride took place. Stirring was continued for an additional ten hours at room temperature. The whole then added to ice-cold hydrochloric acid. The organic layer was washed with water and excess solvent, removed by steam ditillation. The solid obtained was crystallized from the proper solvent to give *2* (Table 1) in about 40 – 70% yield.

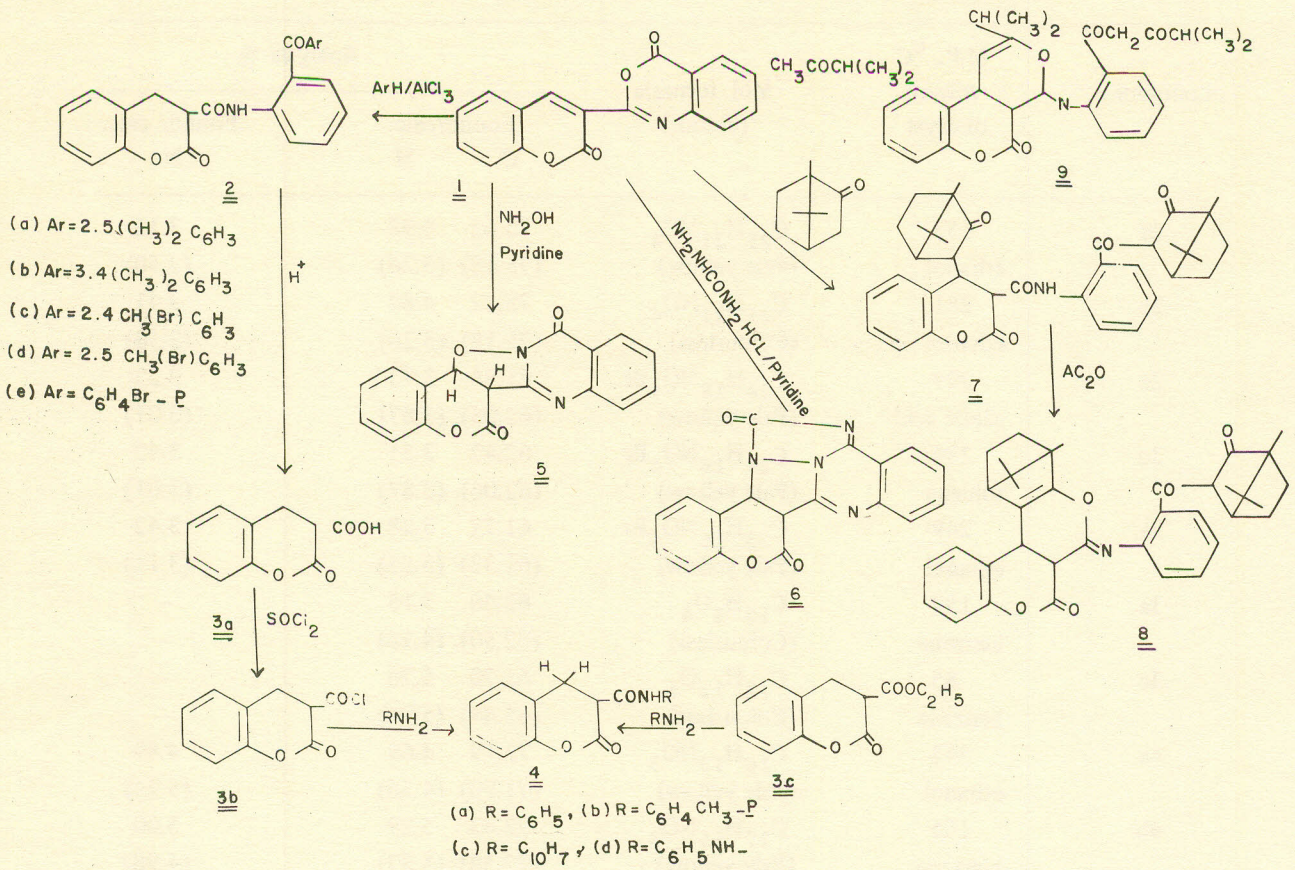
Acid Hydrolysis of 2; Formation of 3 a. A mixture of *2a, 2c* and *2d* (2g), acetic acid (15 ml) and sulphuric acid (10 ml; 70%) was heated for 4 hr., cooled, then poured into water. The solid separated out was filtered off and

Table 1. Characterization data of various compounds prepared.

Compound	M.P. °C solvent of cryst	Mol. formula (colour)	Analysis % Found/calc. C	H	Found/ calc. N
2a	153 ethanol	$C_{25}H_{21}NO_4$ (Pale yellow)	75.62 (75.18)	4.98 (5.26)	3.12 (3.50)
2b	281 ethanol	$C_{25}H_{21}NO_4$ (Colourless)	75.12 (75.18)	4.87 (5.26)	3.41 (3.50)
2c	297 acetic acid	$C_{24}H_{18}NO_4Br$ (Pale yellow)	61.98 (62.06)	3.73 (3.87)	3.22 (3.01)
2d	234 toluene	$C_{24}H_{18}NO_4Br$ (Pale yellow)	62.42 (62.06)	3.51 (3.87)	3.42 (3.01)
2e	249 ethanol	$C_{23}H_{16}NO_4Br$ (Pale yellow)	61.72 (61.33)	3.28 (3.55)	3.42 (3.11)
3a	159 benzene	$C_{10}H_8O_4$ (Colourless)	62.40 (62.50)	3.15 (4.16)	– –
3c	85 benzene	$C_{12}H_{12}O_4$ (Colourless)	65.70 (65.44)	5.76 (5.94)	– –
4a	242 ethanol	$C_{16}H_{13}NO_3$ (Pale yellow)	72.19 (71.90)	4.69 (4.36)	4.89 (5.24)
4b	165 benzene	$C_{17}H_{15}NO_3$ (Pale yellow)	72.43 (72.58)	5.29 (5.37)	5.00 (4.98)
4c	212 ethanol	$C_{20}H_{15}NO_3$ (Pale yellow)	75.90 (75.69)	5.01 (4.76)	4.02 (4.41)
4d	171 benzene	$C_{16}H_{14}N_2O_3$ (yellow)	67.82 (68.08)	5.20 (4.96)	9.50 (9.92)
5	280 toluene	$C_{17}H_{10}N_2O_4$ (Colourless)	66.90 (66.66)	3.42 (3.26)	8.89 (9.15)
6	165 ethanol	$C_{18}H_{10}N_4O_3$ (Pale yellow)	65.62 (65.45)	3.21 (3.03)	17.41 (16.96)
7	286 acetic acid	$C_{37}H_{41}NO_6$ (Colourless)	74.12 (74.62)	7.21 (6.89)	1.98 (2.35)
8	220 acetic acid	$C_{37}H_{39}NO_5$ (Pale yellow)	77.25 (76.94)	6.32 (6.75)	2.73 (2.42)
9	206 ethanol	$C_{27}H_{27}NO_5$ (Colourless)	72.43 (72.80)	6.32 (6.06)	2.99 (3.14)

then crystallized from benzene to give *3a* as colourless crystals m.p. 159° (yield 40%) (Table 1).

Conversion of 3a into 3b then 4 a-d. The 3,4 dihydrocoumarin-3-carboxylic acid *3* a (1.69 m., 0.01 mol) was treated with thionyl chloride (20 ml) to give the acid chloride 3b, after evaporation the excess thionyl chloride. Dry ether (30 ml) and amine namely aniline, P-toluidine, α-naphthylamine and/or phenyl hydrazine were added to *3*b. The mixture was heated on water bath for 2 hr., cooled and poured into water. The residue obtained after separation and evaporation of the ether was crystallized from the proper solvent to give *4*a-d (Table 1) in about 70 – 80%



yield.

Preparation of Authentic Samples of 4 a-d. To a cooled stirred mixture of (9.5 g) of the aluminium chloride and 40 ml of dry *p*-xylene or bromobenzene at 10° was added a solution of the 3-carybethoxycoumarin 4 g; (about 0.02 mol) in 50 ml of the above dry hydrocarbons. The temperature of the reaction mixture was kept at room temperature with stirring for 6 hr., and 3 hr., at the boiling point of the mixture. The complex was decomposed with ice-hydrochloric acid. The organic layer was evaporated and the products were crystallized from benzene to give colourless crystals of *3c* (Table 1).

To a *3c* (1 g; 0.005 mol) and amines namely aniline, *p*-toluidine, α-naphthylamine and phenyl hydrazine (0.01 mol) in ethanol (20 ml) were heated under reflux for 1 hr. On cooling, the products separated were identified as *4* a-d by m.p. and mixed m.p. determination (Table 1).

Base Catalysed Addition Reaction of 1 with Hydroxylamine or Semicarbazide Hydrochloride; Formation of 5 or 6. A mixture of *1* (2.91 g, 0.01 mol) and hydroxylamine hydrochloride or semicarbazide hydrochloride (0.03 mol) in dry pyridine (40 ml) was heated under feflux for 6 hr. The reaction mixture was poured into cold dilute hydrochloric acid to give solid which were crystallized from proper solvent to give *5* ro *6* (Table 1) in about 60 – 70% yielded.

Condensation of 1 with Active Methylene Compounds Formation of 7 or 9. A mixture of *1* (2.91 g, 0.01 mol), camphor or methyl isopropyl ketone (0.02 mol) and sodium ethoxide (0.03 mol) was heated at 170° for 6 hr. Then poured upon water. The product separated out, was filtered off and recrystallized from the suitable solvent to give *7* and *9* respectively (Table 1) in 50% yield.

Conversion of 7 into 8. A mixture of *7* (2 g) and acetic anhydride (25 ml) was refluxed for 2 hr., cooled and stirred into cold water (100 ml). The residue was filtered off and crystallized from acetic acid to give *8* (Table 1) in about 40% yield.

REFERENCES

1. M.M. Abdalla, M. El-Kady and A.F. El-Farargy, Egypt J. Chem., **20**, 245 (1977).
2. M.A. El-Hashash, M.A. Sayed, Egypt J. Chem., **21**, 115 (1978).
3. M.A. El-Hashash, M.A. Hassan and M.A. El-Sayed, Pakistan J. Sci. Ind. Res., **20**, 336 (1977).
4. M.A. El-Hashash, A.M. Kaddah, M. El-Kady and M.M. Ammer, Pakistan J. Sci. Ind. Res., **25** (1982).
5. A. Sammour, A.F.M. Fahmy and M. Mahmoud, Indian J. Chem., **11**, 222 (1973).
6. A. Sammour, M.I.B. Selim and M. El-Kady, U.A.R. J. Chem., **14**, 261 (1971).
7. A. Sammour, M. Abdalla and M. El-Kady, Acta Chim. Hung. Budapest, **82**, 369 (1974).
8. A. Sammour and M. El-Kady, Indian J. Chem., **12**, 51 (1974).