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Synthesis of Some Quinazolines and Imidazolo-[1,5-a]-3,1-benzoxazine-4-one Derivatives

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ABSTRACT

Some substituted N-methylene-2-(3,1-benzoxazonyl-4-one) amide (3a-c) were prepared from reaction of acetic anhydride with N-acyl anthranilic acid (2a-c) was synthesized from anthranilic acid with acyl glycinyl chloride. Treatment of (3a-c) with $POCl_3$ gave imidazolo-[1,5-a]-3,1-benzoxazin-4-one (4a-c).

Quinazoline derivatives (6a-c) were prepared by reaction of methyl anthranilate with imidoyl chloride, the resulting esters were then converted to the hydrazides (7a-c). The synthesized compounds were identificated by IR and UV spectra.

تحضير بعض مشتقات الكوينازولين والاميدازولو-[1,5-a]-3،1-بنزوكسازين-4-اون

الملخص

تم تحضير عدد من معوضات N-مثيلين-2-(3،1-بنزوكسازونايل-4-اون) معوض اميد (3a-c) من تفاعل انهيدريد الخليك مع N-اسيل حامض الانثرانيليك (2a-c) والمحضر من تفاعل حامض الانثرانيليك مع اسيل كلاسينايل كلوريد. ثم عومات المركبات (3a-c) مع $POCl_3$ للحصول على اميدازولو [1,5-a]-1،3-بنزوكسازين-4-اون (4a-c). كما تم تحضير عدد من معوضات الكوينازولين (6a-c) من تفاعل انثرانيليت المثيل مع الاميدوايل كلوريد والمحضر من تفاعل اسيل كلايسين اثيل استر مع PCl_5، ثم تم تحويل الاسترات الناتجة الى الهيدرازيدات المقابلة (7a-c) من خلال تفاعلها مع الهيدرازين المائي. تم تشخيص المركبات المحضرة باستخدام اطياف الاشعة تحت الحمراء (IR) وفوق البنفسجية (UV).

INTRODUCTION

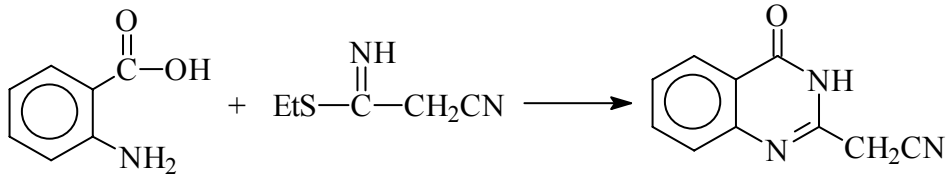
Quinazoline and benzoxazine compounds are of interest in research for biologically active compounds. They have antimicrobial activity (Habib et al., 1995) and traumatic brain treatment (Chenard and Shenk, 1999). Among them there are compounds displaying analgesic (Wolf and Dutty, 1975), antiparkinson (Tiwari and Satsangi, 1978) and anticonvulsant properties (Suesse, 1981). These compounds were widely used in the

synthesis of dyestuffs of various classes including styrenes (Yamada et al., 1974) and azo dyes (Dimroth and Lotsch, 1982).

2-Substituted-3,1-benzoxazine derivatives were prepared usually by heating of anthranilic acid with acid chloride in dry pyridine (Ameta et al., 2006) or acid anhydride. (Madkour, 2003).

Coppola and Schuster (1989) used phosgene with substituted anthranilic acid, to give isatoic anhydride. Jackson and Marriott (2002) used Ac_2O/NaOAc with acyl anthranilic to prepare the benzoxazine.

Among the published methods for preparing quinazoline, the reaction of 1-(2-bromobenzoyl)-3-phenyl thoiurea with potassium tert-butoxide in dry dimethyl formamide leads to formation of 1-phenyl-2-thioquinazolin-4-one (Bowman et al., 2003). 4-Aminoquinazolines were prepared when N,N-dimethyl-N`-(o-cyanophenyl) formamidine treated with ammonium acetate (Deshpande and Seshadri, 1973). Reaction of α-cyano ethyl thioiminoacetate with substituted anthranilic acid gave α-quinazolinyl acetonitrile (Voloven et al., 2002).



Papadopoulos (1981) prepared imidazol-[2,3-c]-quinazoline from intereaction of 4-imino-3-ethoxy carbonyl methylene quinazoline-2-one in basic media.

Finally, quinazoline was prepared from the reaction of 2-aminobenzamide with benzonitrile in microwave irradiation in presence of potassium tert-butoxide (Seijas et al., 2002).

EXPERIMENTAL

All melting points were determined using Electrothermal 9300 melting point apparatus. IR spectra were performed using Brucker F.T.I.R. instrument as KBr disc. UV spectra were recorded on Shimadzu double-beam spectrophotometer UV-210 A using acetone as a solvent. N-Acyl glycine (comp. 1a-c) and N-acyl glycine ethyl ester (comp. 5a-c) were prepared according to the published procedure (Basheer, 2000).

Synthesis of N-acyl anthranilic acid (2a-c) (Jackson and Marriott,2002)

To a mixture of (0.01 mole, 1.37 gm) of anthranilic acid and (0.01 mole, 1 gm) of triethyl amine in (50 ml) of benzene, (0.01 mole) N-acyl glycinyl chloride in (20 ml) of benzene was added dropwise with stirring for (30 min). The mixture was refluxed for (2 hr), cooled, evaporated the solvent and recrystallized from ethanol. The melting point and spectral data were shown in Table (1).

Synthesis of N[2-(3,1-benzoxazonyl-4-one) methylene amides (3a-c) (Madkour, 2003)

(0.01 mole) of compounds (2a-c) in (20 ml) of acetic anhydride was refluxed for (2 hrs). The solution was concentrated to half by distillation of acetic anhydride under reduced pressure. The product was filtered, dried and recrystallized from (50%) ethanol. Physical properties and spectral data were shown in Table (2).

Synthesis of imidazolo-[1,5-a]-3,1-benzoxazin-4-one(4a-c) (Grimmett, 1997)

(0.005 mole) of compounds (3a-c) and (2 ml) of phosphorous oxychloride was heated on a steam bath for (3 hrs) under anhydrous conditions. Then, the excess of $POCl_3$ was evaporated under reduced pressure, and (10 ml) of (5%) sodium hydroxide solution was added to neutralize pH. The solution was extracted with (20 ml) of chloroform, evaporation of the solvent give solid which were recrystallized from ethanol. Melting points and spectral data were indicated in Table (3).

Synthesis of ethyl [3-(2-substituted) quinazolinyl-4-one] acetate (6a-c) (Scherrer and Beatty, 1972)

A mixture of ethyl-N-acyl glycinate (5a-c) (0.01 mole) and (0.01 mole, 2.08 gm) of phosphorous pentachloride was heated at (90 °C) for (2 hrs), removal of $POCl_3$ under reduced pressure gave imidoyl chloride. Then (0.01 mole, 1.51 gm) of methyl anthranilate in (20 ml) of dry dimethyl formamide was added and allowed to stand overnight at room temperature, heating the mixture for (10 min) at (100 °C), then cooled and diluted with ethanol (30 ml) and water (20 ml). The precipitate was filtered and recrystallized from (50%) ethanol. The melting points and spectral data were indicated in Table (4).

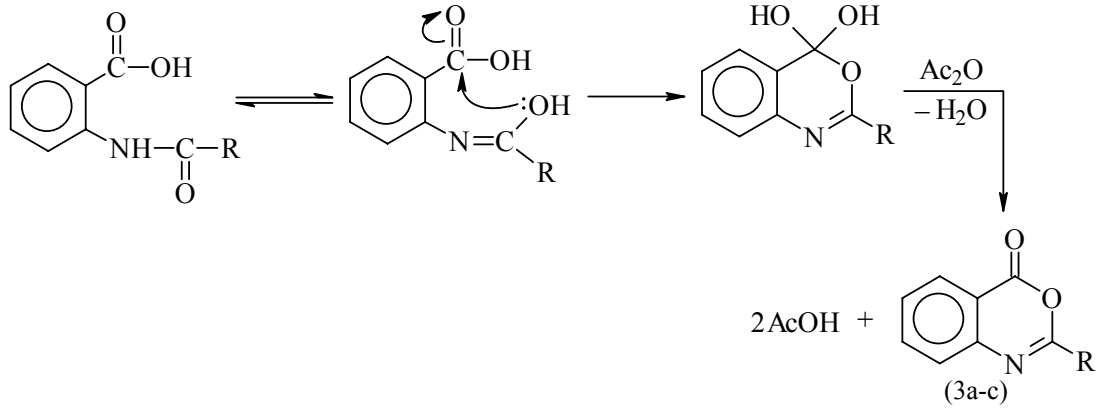
Synthesis of α-[3-(2-substituted) quinazolinyl-4-one]-acetyl hydrazine (7a-c) (Yale et al., 1953)

A mixture of (0.005 mole) of (6a-c) and (0.02 mole) of hydrazine hydrate in (20 ml) of ethanol was refluxed for (3 hrs), then cooled, filtered off and recrystallized from ethanol. Physical properties and spectral data are presented in Table (5).

RESULTS AND DISCUSSION

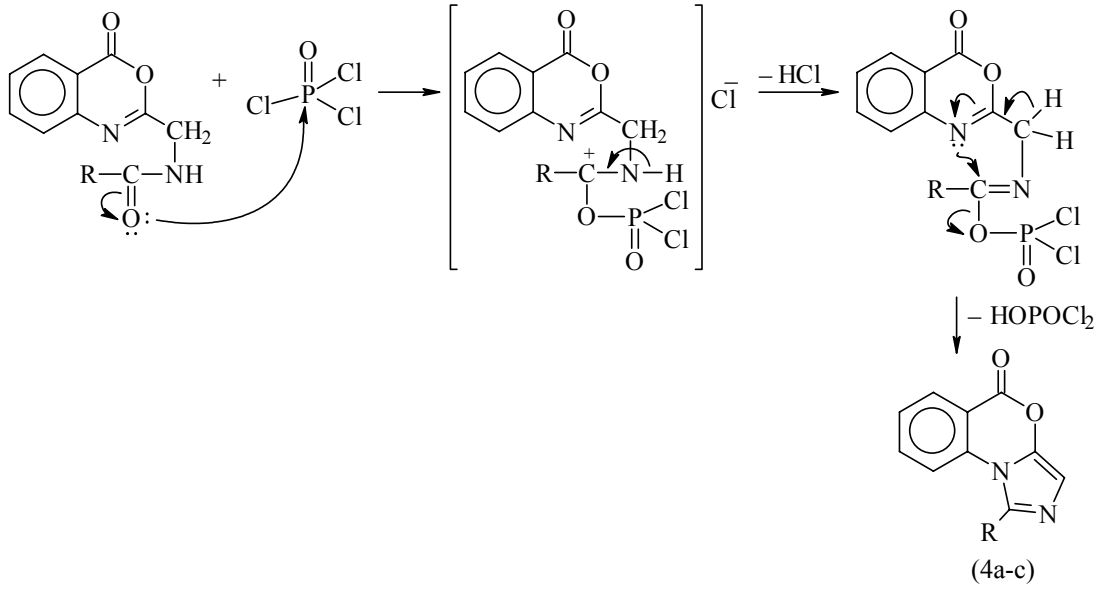
The compounds (2a-c) were prepared by the reaction of anthranilic acid with N-acyl glycinyl chloride in presence of Et_3N. the IR spectra showed bands at (1616-1649 cm^{-1}) for (C=O) amide, (1701 cm^{-1}) for (C=O) acid, (3216-3379 cm^{-1}) for (O-H) and (3444-3457 cm^{-1}) for (N-H).

Substituted 3,1-benzoxazine-4-one (3a-c) were synthesized by the condensation of compounds (2a-c) with acetic anhydride followed by ring closer. The suggested mechanism could be illustrated as follow:



The obtained products (3a-c) were identified by the IR and UV spectral data which were indicated in Table (2).

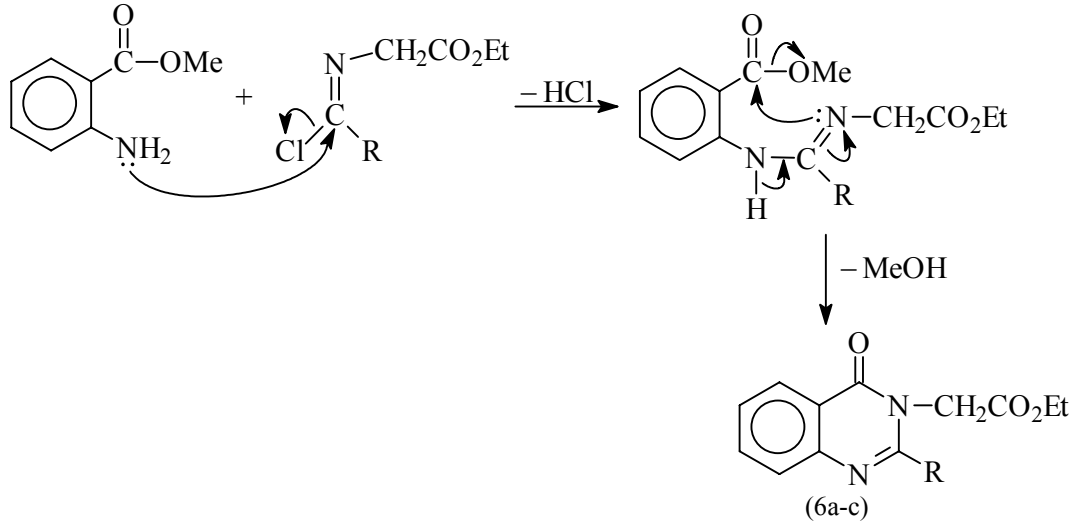
When compounds (3a-c) were treated with $POCl_3$ in dry conditions imidazolo-[1,5-a]-3,1-benzoxazine-4-one (4a-c) were obtained. The suggested cyclization mechanism can be illustrated as following.



(4a-c)

The IR spectra of final compounds (4a-c) showed three main bands for the stretching vibration of (C-O), (C=N) and (C=O) at (1013-1065 cm^{-1}), (1638-1656 cm^{-1}) and (1690-1706 cm^{-1}). UV spectra showed increasing in λ_{max} (bathochromic shift) (326-334 nm) compared with copounds (3a-c) due to appearance of the conjugation effect on the $n \rightarrow \pi^*$ transition as shown in Table (3) (Silverstein et al., 1974).

The Synthesis of ethyl [3-(2-substituted) quinazolinyl-4-one] acetate (6a-c) were prepared by the reaction of methyl anthranilate with N-ethoxy carbonyl methyl imidoyl chloride (prepared from N-acyl glycine ethyl ester with PCl_5) in dry DMF at room temperature. The cyclization mechanism for the formation of these compounds could be represented by simple nucleophilic substitution reaction in which the lone pair of amino group attack the imine carbone in imidoyl chloride followed by nucleophilic attack of nitrogen toward the near by carbonyl of ester, as shown below in the suggested mechanism.



(6a-c)

The IR spectra of compound (6a-c) showed stretching vibration bands at (1081-1112 cm^{-1}), (1627-1641 cm^{-1}), (1671-1684 cm^{-1}) and (1716-1733 cm^{-1}) related to (C-O), (C=N), (C=O amide) and (C=O ester) groups respectively. UV spectra showed λ_{max} at (338-356 nm) which due to $n \rightarrow \pi^*$ transitions as shown in Table (4).

Compounds (7a-c) were prepared by the reaction of compounds (6a-c) with hydrazine hydrate in ethanol by nucleophilic attack of amino group of hydrazine on ester carbonyl followed by elimination of ethanol molecule.

The synthesized compounds showed bands at (1604-1615 cm^{-1}) due to (C=N), (1674-1684 cm^{-1}) for (C=O) and (3308-3338 cm^{-1}) for (N-H). UV spectra showed increasing in λ_{max} (bathochromic shift) (349-360 nm) compared with compounds (6a-c) due to appearance of resonance effect which affected the $n \rightarrow \pi^*$ transition as shown in Table (5) (Silverstein et al., 1974).

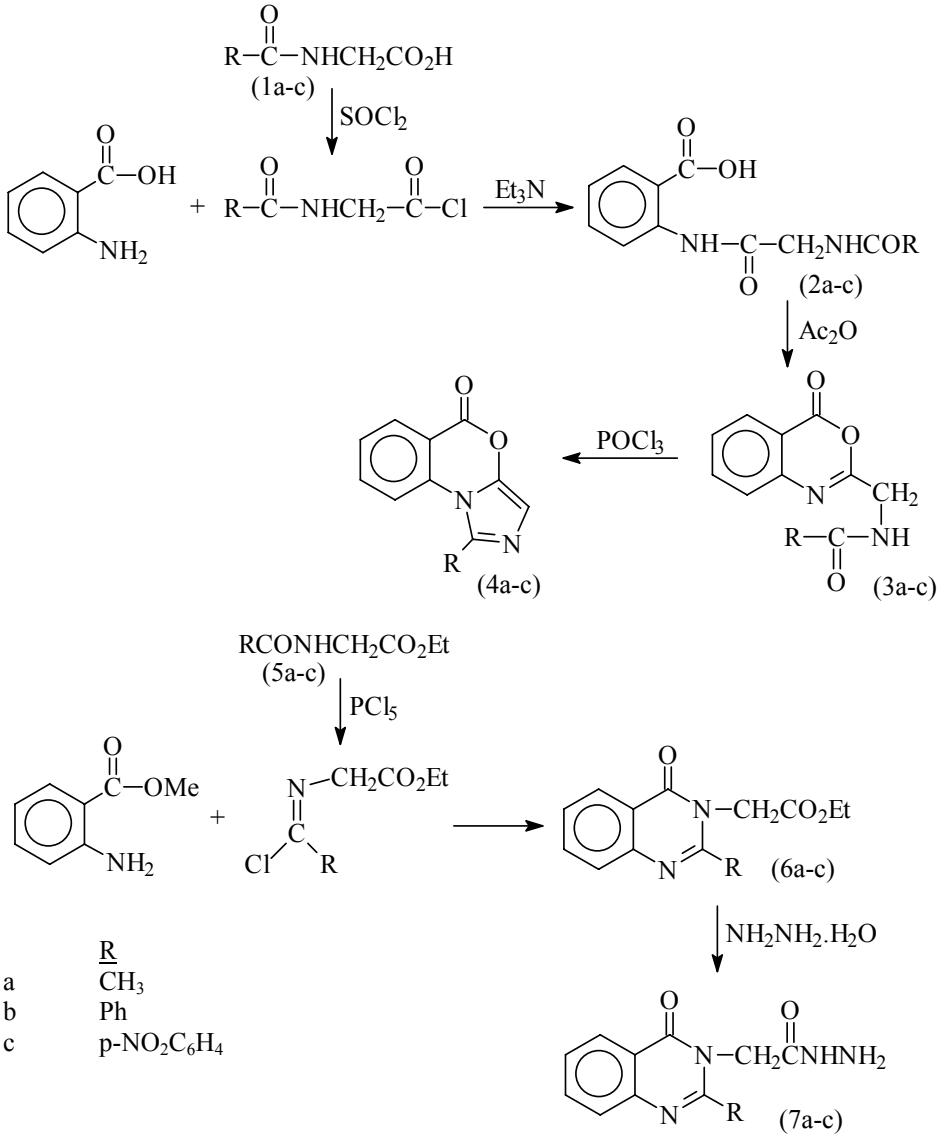


Table 1: Physical and spectral data of compounds (2a-c)

Comp. No.	m.p. °C	Yield %	IR ν cm^{-1}				U.V λ_{max} (nm)
			C=O amide	C=O acid	O-H	N-H	
2a	152-153	77	1626	1701	3362	3457	280
2b	204-206	68	1616	1704	3216	3444	321
2c	232-233	80	1649	1712	3379	3449	322

Table 2: Physical and spectral data of compounds (3a-c)

Comp. No.	m.p. °C	Yield %	IR ν cm^{-1}					U.V λ_{max} (nm)
			C-O	C=N, C⋯C	C=O amide	C=O	N-H	
3a	172-173	62	1041	1604	1646 , 1683	1716	3566	326
3b	161-162	75	1035	1606	1639 , 1679	1699	3516	332
3c	179-180	69	1108	1607	1654 , 1681	1697	3489	334

Table 3: Physical and spectral data of compounds (4a-c)

Comp. No.	m.p. °C	Yield %	IR ν cm^{-1}				U.V λ_{max} (nm)
			C-O	C⋯C	C=N	C=O	
4a	159-160	68	1048	1604	1656	1706	332
4b	92-93	71	1065	1607	1653	1695	326
4c	110-112	64	1013	1598	1638	1690	334

Table 4: Physical and spectral data of compounds (6a-c)

Comp. No.	m.p. °C	Yield %	IR ν cm^{-1}				U.V λ_{max} (nm)
			C-O	C=N	C=O amide	C=O ester	
6a	198-199	73	1112	1641	1678	1726	338
6b	96-98	70	1081	1636	1671	1733	340
6c	182-184	79	1105	1627	1684	1716	356

Table 5: Physical and spectral data of compounds (7a-c)

Comp. No.	m.p. °C	Yield %	IR ν cm^{-1}				U.V λ_{max} (nm)
			C=N	C=O amide	C=O hydra.	N-H	
7a	108-110	80	1608	1681	1634	3332	349
7b	190-191	76	1604	1674	1639	3338	352
7c	209-210	81	1615	1684	1667	3308	360

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