Alkyl Heteroaromatics as Building Blocks in Organic Synthesis: The Reactivity of Alkyl Azoles toward Electrophilic Reagents

I. S. Abdel Hafiz[a], A. A. Hassanien[a], and A. M. Hussein[b,*]

[a] Department of Chemistry, Faculty of Education, Suez Canal University, Arish, Egypt
[b] Department of Chemistry, Faculty of Science, Al-Azhar University, Assiut 71524, Egypt

* Reprint requests to Dr. A. M. Hussein. Fax: 002 088 325436.
E-mail: haleem_m_h@hotmail.com

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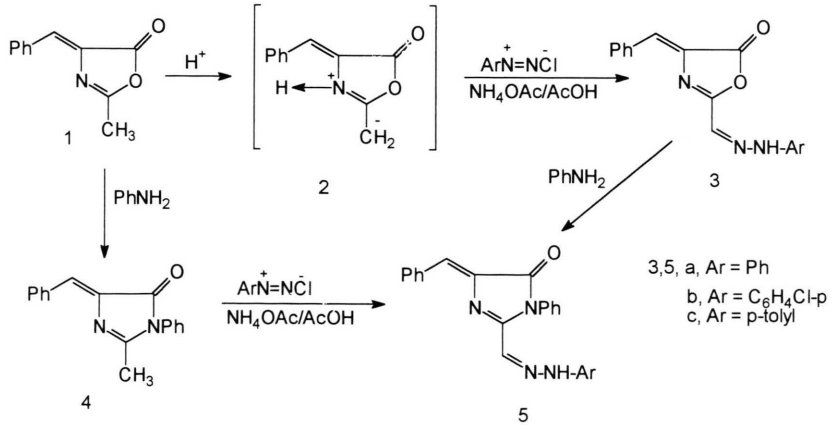
Oxazolone **(1)** couples with aromatic diazonium salts to yield the arylhydrazones **(3a-c)**. Compound **3** reacts with aniline to give aryl hydrazone **(5).** Compound **5** was also obtained *via* converting **1** into the imidazolone **(4)** and subsequent treatment of **4** with aromatic diazonium salts. Compounds **1** and **12** reacted with arylidenemalononitrile **(6)** to yield compounds **8** and **14** respectively. Also compounds **1, 12** condensed with an aromatic aldehydes to yield **11** and **17**. Compounds **11, 17** reacted further with one molecule of malononitrile to give compounds **8** and **14,** respectively. Compound **20** which was generated *in situ* by heating phenacylthiocyanate **(19)** in acetic anhydride on treatment with hydrazine hydrate or phenyl hydrazine gives **21** and **22** respectively. Also **20** reacted with malononitrile or with ethyl cyanoacetate to give **23** and **24,** respectively.

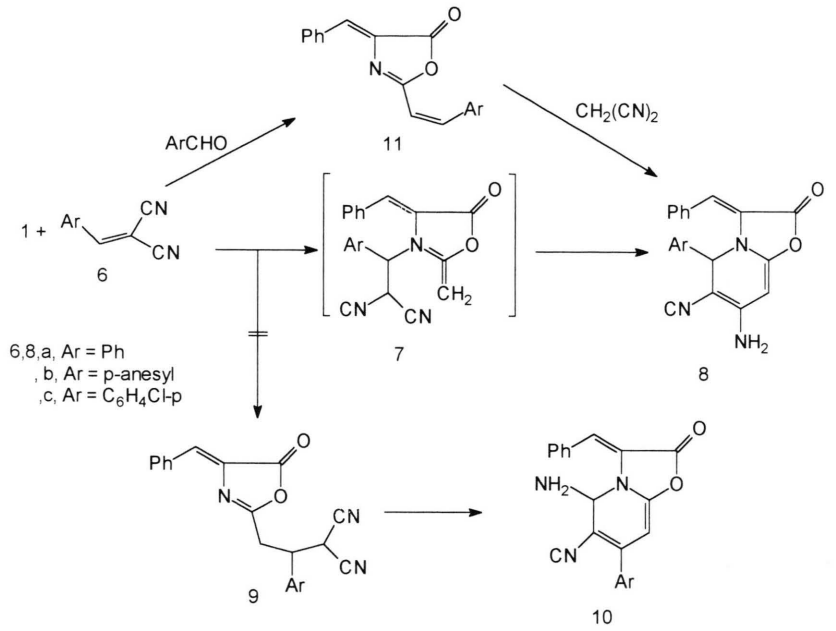
Alkyl functions in π-deficient alkylheteroaromatics are reactive toward electrophiles under mild conditions [1–3]. This reactivity has been extensively utilized for the synthesis of otherwise not readily obtainable heterocyclic derivatives [4–6]. We investigated the reactivity of an alkyl function in 2-methyl-4-benzylidene-2-oxazolin-5-one **(1)** and 2-methyl-1,3-benzoxazin-3-one **(12)** toward electrophilic reagents. Also work, aimed at the exploration of the potential of thiazolone as precursors for polyfunctionally substituted heteroaromatics, is reported here. So, we have found that the methyl function in **1** readily couples with aromatic diazonium salts in acetic acid solution and in presence of ammonium acetate to yield the corresponding arylhydrazones **(3a-c)**. Compound **3a** reacted with aniline to give the arylhydrazone **(5)**. Compound **5** was also obtained *via* converting **1** into the imidazolone **(4),** utilizing a literature procedure [7], and subsequent treatment of **4** with aromatic diazonium salts (*c.f.* Scheme 1).



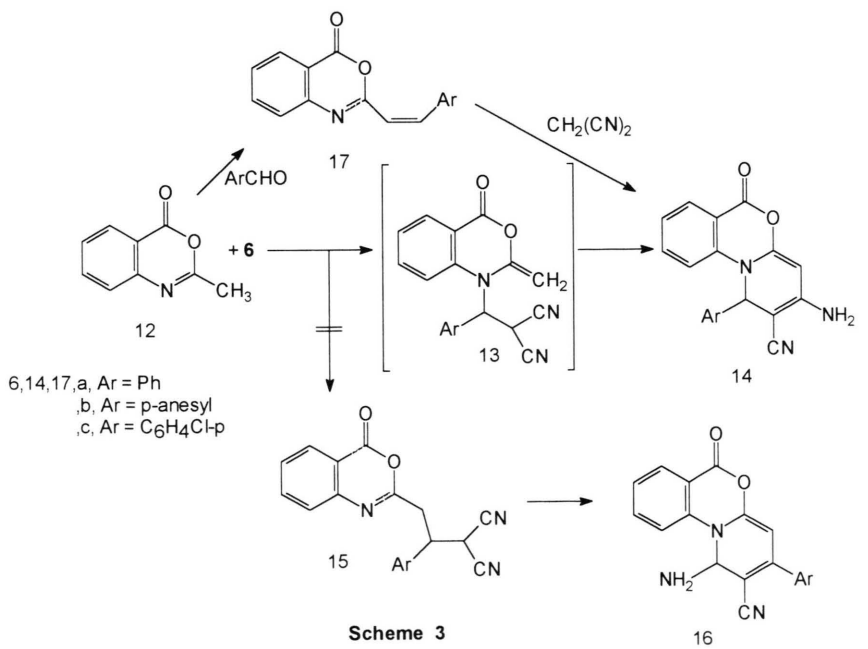
Scheme 1

0932–0776/99/0700–0923 $06.00

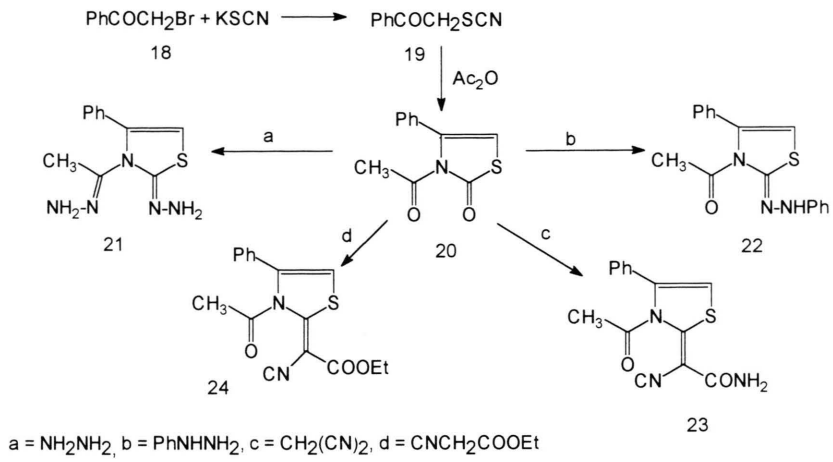
Trials to couple **12** with aromatic diazonium salts failed. This can be rationalized in terms of the great instability of such a structure in aqueous medium [8]. Although the alkyl function in heteroaromatic azoles has been previously shown to be active toward carbon electrophiles, to our knowledge, this is the first reported reaction of methyl azole derivatives with aryldiazonium salts. It is of a value to report that coupling took place only in acetic acid and in presence of ammonium acetate.



Scheme 2



Scheme 3



Scheme 4

In media like EtOH/NaOAc, pyridine or EtOH/NaOH, no coupling was observed. We do believe that the presence of acetic acid is essential to protonate the ring nitrogen and that the Zwitter ion **2** is the reactive species.

Compound **1** reacted with arylidenemalononitrile **(6)** in acetic acid and in presence of sodium acetate to yield 1:1 adducts. These may be formulated as **8** or isomeric **10**. Acyclic products **(7)** were ruled out based on ^{1}H NMR which did not reveal expected multiplets for protons linked to a sp^3 carbon. Structure **8** is preferred over **10** as demonstrated by ^{1}H NMR which revealed a dihydropyridine proton at δ 6.45. Isomeric **10** should show these protons at much higher field (*ca.* 5.0 ppm). Compound **8** was also obtained *via* reaction of **1** with an aromatic aldehyde to yield **11.** Subsequent reaction of **11** with one mole of malononitrile to yielded **8.**

Similarly, compound **12** was reacted with arylidenemalononitrile **(6)** in acetic acid and in presence of sodium acetate to yield 1:1 adducts. These may be formulated as **14** or isomeric **16**. Structure **14** is the main product based on spectral data. Compound **14** was also obtained *via* reaction of **12** with the aromatic aldehyde to yield **17** and subsequent reaction of **17** with one mole of malononitrile to give **14**.

Compound **20** was generated *in situ* by heating phenacyl thiocyanate **(19)** in acetic anhydride for a short period. This compound afforded compound **21** on treatment with hydrazine hydrate in ethanolic solution. Also it reacted with phenyl hydrazine to give compound **22**. The reaction of **20** with active methylene shows that **23** affords with malononitrile in ethanolic triethylamine compound and with ethyl cyanoacetate to yield **24**.

Experimental

Melting points (uncorrected) were measured on a Gallenkamp apparatus. IR spectra of KBr discs recorded on a FT IR-820 IPC infrared spectrophotometer Shimadzu (ν, cm^{-1}). ^{1}H NMR spectra were recorded for $CDCl_3$ solution on a Varian T-60 NMR spectrometer using Me4Si as an internal reference. Mass spectra were recorded on a GCMS-QP 1000 Ex spectrometer. Elemental analysis were carried out at the microanalytical laboratory, University of Cairo. Melting points, percentage yields and analytical data of the compounds are listed in Tables I and II.

Preparation of aryl hydrazones **3a-c**

A solution of diazotized amines (prepared from 0.01 mol of aromatic amines and appropriate quantities of sodium nitrite and hydrochloric acid) was added to 0.01 mol of methyloxazolinone **(1)** in 100 ml acetic acid and 4.0 g ammonium acetate. The reaction mixture was stirred in an ice-bath for 3 h. The solid product was washed with water, filtered off, and crystallized from the proper solvent.

4-Benzylidene-3-methyl-2-imidazol-5-one **4**

To a solution of **1** (0.01 mol) in pyridine (20 ml), the appropriate amount of aniline (0.01 mol) was

Table I. Yields, melting points, and elemental analysis of the new compounds.

Comp.	M.p. [°C]	Solvent	Colour	Yield [%]	Molecular formula (MS)	Calcd (Found) [%] C	H	N
3a	227	EtOH	red	50	$C_{17}H_{13}N_3O_2$ (290)	70.1 (70.2)	4.46 (4.6)	14.43 (14.5)
3b	205	EtOH	brown	65	$C_{17}H_{12}N_5O_2Cl$ (325)	62.67 (62.8)	3.68 (3.7)	12.90 (13.1)
3c	217	EtOH	red	62	$C_{18}H_{15}N_3O_2$ (304)	70.08 (70.3)	4.91 (5.0)	13.77 13.9
5	168	EtOH	brown	75	$C_{23}H_{18}N_4O$ (366)	75.4 (75.7)	4.91 (5.2)	5.30 (5.5)
8a	180	EtOH	yellow	65	$C_{21}H_{15}N_3O_2$ (341)	73.9 (74.1)	4.39 (4.5)	12.31 (12.5)
8b	175	EtOH	yellow	78	$C_{22}H_{17}N_3O_3$ (370)	71.15 (71.3)	4.58 (4.7)	11.32 (11.6)
8c	190	EtOH	yellow	70	$C_{12}H_{14}N_5O_2Cl$ (375)	67.11 (67.2)	3.73 (3.9)	11.18 (11.3)
11a	80	EtOH	brown	80	$C_{18}H_{13}NO_2$ (276)	78.74 (78.9)	4.72 4.9	5.09 (5.2)
11b	172	EtOH	yellow	75	$C_{19}H_{15}NO_3$ (306)	74.75 (75.0)	4.91 (5.2)	4.59 (4.7)
11c	188	EtOH	buff	78	$C_{18}H_{12}NO_2Cl$ (310)	69.78 (70.0)	3.87 (4.0)	4.52 (4.6)
14a	240	EtOH	brown	50	$C_{19}H_{13}N_3O_2$ (315)	72.38 (72.6)	4.12 (4.3)	13.33 (13.5)
14b	210	EtOH	yellow	55	$C_{20}H_{15}N_3O_3$ (344)	69.56 (69.7)	4.34 (4.4)	12.17 (12.3)
14c	268	EtOH/ DMF	yellow	60	$C_{19}H_{12}N_3O_2Cl$ (350)	65.23 (65.4)	3.43 (4.6)	12.01 (12.2)
17a	140	EtOH	buff	62	$C_{16}H_{11}NO_2$ (249)	77.10 (77.3)	4.41 (4.5)	5.62 (5.8)
17b	206	EtOH	colourless	72	$C_{17}H_{13}NO_3$ (279)	73.11 (73.3)	4.65 (4.8)	5.01 (5.3)
17c	185	EtOH	colourless	65	$C_{16}H_{10}NO_2Cl$ (287)	67.72 (67.9)	3.52 (3.7)	4.93 (5.1)
20	135	EtOH	colourless	70	$C_{11}H_9NO_2S$ (219)	60.26 (60.4)	4.14 (4.2)	6.39 (6.4)
21	128	EtOH	colourless	65	$C_{11}H_{15}N_5S$ (249)	52.99 (53.2)	6.06 (6.2)	28.09 (28.3)
22	185	EtOH	Yellow	68	$C_{17}H_{15}N_3OS$ (309)	66.00 (66.2)	4.89 (5.0)	13.58 (13..7)
23	260	EtOH/ DMF	colourless	75	$C_{14}H_{11}N_3O_2S$ (285)	58.94 (59.1)	3.89 (4.0)	14.73 (14.9)
24	212	EtOH	Yellow	78	$C_{16}H_{14}N_2O_3S$ (314)	61.13 (61.3)	4.49 (4.6)	8.91 (9.1)

added. The reaction mixture was refluxed for five hours and then evaporated *in vacuo*. The remaining product is poured on ice, acidified by hydrochloric acid. The solid product was collected by filtration and crystallized from ethanol.

Preparation of aryl hydrazone **5**

Method (A): A solution of benzene diazonium salt (prepared from 0.01 mol of aniline and the appropriate quantities of sodium nitrite and hydrochloric acid) was added (0.01) mol of methylimidazolinone **(4)** in 100 ml acetic acid and 4.0 g ammonium acetate. The reaction mixture was stirred in ice-bath for 3 h. The solid product was washed with water, filtered off, and crystallized from ethanol.

Method (B): To a solution of **3a** (0.01 mol) in pyridine (20 ml), the appropriate amount of aniline (0.01 mol) was added. The reaction mixture was refluxed for five hours and then evaporated *in vacuo*. The remaining product was poured on ice/water, acidified by hydrochloric acid. The solid

Table II. Spectroscopic data of new compounds.

Comp.	IR [cm^{-1}]	^1H NMR
3a	3306–3212 (NH_2), 1689 (CO), 1631 (C=N)	4.65(s,1H,CH), 7.0–7.8 (m,11H, Ar-H), 9.5 (s, 1H, NH)
3b	3330–3055 (NH), 1776 (CO), 1630 (C=N)	4.6 (s, 1H, CH), 7.0–7.6 (m, 10H, Ar-H), 9.5 (s, 1H, NH)
3c	3240–3100 (NH), 1680 (CO)	2.7 (s,3H, CH_3), 4.6 (s, 1H, CH), 7.0–7.6 (m, 10H, Ar -H), 9.8 (s, 1H, NH)
5	3307–3120 (NH), 1690 (CO)	4.6 (s, 1H, CH), 7.0–7.7 (m, 16H, Ar-H), 9.7 (s,1H, NH)
8a	3360–3100 (NH_2), 2210 (CN), 1700 (CO)	6.4 (s, 1H, 2H-pyridine), 7.3–7.55 (m, 12H, Ar-H), 9.8 (s, 2H, NH_2)
8b	3340–3110 (NH_2), 2214 (CN), 1672 (CO)	3.4 (s, 3H, CH_3), 4.6 (s, 1H, CH), 6.6 (s, 1H, 2H-pyridine), 7.3–7.5 (m, 10H, Ar-H), 8.7 (d, 2H, NH_2)
8c	3454–3200 (NH_2), 2212 (CN), 1701 (CO)	4.5 (s, 1H, CH), 5.6 (s, 1H, 2H-pyridine), 7.4–8.0 (m, 10H, Ar-H), 12.2 (s, 2H, NH_2)
11a	3060–3030 (Ar-CH), 1732 (CO)	4.3 (s, 1H, CH), 6.3 (d, 1H, CH), 6.6 (d, 1H, CH), 7.2–7.9 (m, 10H, Ar-H)
11b	3050–3030 (Ar-CH), 1725 (CO)	.3.4 (s,3H,CH_3), 4.33 (s, 1H, CH), 6.2 (d, 1H, CH), 6.6 (d, 1H, CH), 7.2–7.7 (m, 9H, Ar-H)
11c	3050–3030 (Ar-CH), 1728 (CO)	.4,4 (s, 1H, CH), 6.0 (d, 1H, CH), 6.4 (d, 1H, CH), 7.2–7.6 (m, 9H, Ar-H)
14a	3350–3180 (NH_2), 2200 (CN), 1700 (CO)	7.0 (s,1H, 2H-pyridine), 7.4–8.2 (m, 10H, Ar-H), 12.3 (s,2H, NH_2)
14b	3340–3170 (NH_2), 2210 (CN), 1700 (CO)	3.5 (s,3H, CH_3), 7.0–7.1 (s, 1H, 2H-pyridine), 7.4–8.0 (m, 9H, Ar-H), 12.2 (s, 2H, NH_2)
14c	3345–3155 (NH_2), 1705 (CO)	7.0–7.2 (s, 1H, 2H-pyridine), 7.4–8.2 (m, 9H, Ar-H), 12.3 (s,2H, NH_2)
17a	3070–3008 (Ar-CH), 1762 (CO), 1640 (C=N)	6.3 (d, 1H, CH), 6.6 (d, 1H, CH), 7.2–7.9 (m, 9H, Ar-H)
17b	3060–3000 (Ar-CH), 1750 (CO), 1634 (C=N)	2.9 (s, 3H, CH_3), 6.4(d, 1H, CH), 6.8 (d, 1H, CH), 7.2–7.9 (m, 8H, Ar-H)
17c	3080–3000 (Ar-CH), 1782 (CO), 1645 (C=N)	6.5 (d, 1H, CH), 6.9 (d, 1H, CH), 7.2–7.9 (m, 8H, Ar-H)
20	1660 (CO), 1670 (CO)	2.4 (s, 3H, CH_3), 6.8 (s, 1H, thiazole-H), 7.4–7.8 (m, 5H, Ar-H)
21	3359–3126(NH_2)	2.2 (s, 3H, CH_3), 6.9 (s, 1H, thiazole-H), 7.4–8.0 (m, 9H, Ar-H and NH_2)
22	3220 (NH), 1670 (CO)	2.4 (s, 3H, CH_3), 6.8 (s, 1H, thiazole-H), 72–7.9 (m, 10H, Ar-H), 9.8 (s, 1H, NH)
23	3415–3300 (NH_2), 2221 (CN), 1703 (amidic CO0, 1691 (ring CO)	2.2 (s, 3H, CH_3), 6.8 (s, 1H, thiazole-H), 72–7.9 (m, 7H, Ar-H and NH_2)
24	2204 (CN), 1720 (ester CO), 1678 (ring CO)	1.2 (t, 3H, CH_3), 2.4 (s, 3H, CH_3), 4.2 (q, 2H, CH_2), 7.1 (s, 1H, thiazole-H), 75–7.9 (m, 5H, Ar-H)

product was washed with water and crystallized from ethanol.

Preparation of condensed pyridines **8a-c** *and* **14a-c**. *General procedure*

To a solution of **1** or **12** (0.01 mol) in acetic acid (50 ml), 4 g of sodium acetate and the appropriate **6a-c** (0.01 mol) were added. The reaction mixture was refluxed for 5 h and then evaporated *in vacuo*. The remaining product was poured on ice and neutralized by sodium carbonate. The solid product was then collected by filtration and crystallized from the proper solvent.

Reaction of **1** *and* **12** *with aromatic aldehydes. General procedure*

To a solution of **1** or **12** (0.01 mol) in acetic acid (50 ml), 4 g of sodium acetate and the appropriate aromatic aldehyde (0,01 mol) were added. The reaction mixture was refluxed for 5 h and then evaporated *in vacuo*. The remaining product was poured on ice and neutralized by sodium carbonate. The solid product was then collected by filtration and crystallized from ethanol.

Preparation of thiazolone **20**

2 g of the thiocyanate derivative **19** (0.01 mol) were dissolved in 20 ml acetic anhydride and

heated under reflux for 1 h, then left to stand and poured on water. The solid product formed after standing overnight was filtered off and recrystallized from ethanol as colorless crystals.

Preparation of compounds **21** *and* **22**. *General procedure*

To a solution of **20** (0.01 mol) in ethanol (30 ml), the hydrazine hydrate or phenyl hydrazine (0.01 mol) was added. The reaction mixture was refluxed for 3h and then left to overnight at room temperature. The solid product was filtered off and recrystallized from ethanol as yellow crystals.

Reaction of **20** *with active methylene*. *General procedure*

Equimolar amounts of **20** and malononitrile or ethyl cyanoacetate in ethanol (30 ml) were treated with little amount of triethylamine. The reaction mixture was refluxed for 3 h and then left to overnight at room temperature. The precipitate formed was collected by filtration and recrystallized from ethanol.

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