1,4–DIPOLAR CYCLOADDITION REACTIONS IN ORGANIC SYNTHESIS: SYNTHESIS OF SOME NEW N–ARYLPHTHALIMIDES AND FULLY SUBSTITUTED PYRROLO[3,4-H] QUINOLINE DERIVATIVES

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Abstract:

N-Arylphthalimides **3a–e** were prepared through the reaction of 2–mino-3-cyano-4-ethoxycarbonyl-5-methylfuran **1** and N-Arylmaleimides **2a–e**. Compounds **3a–e** reacted with malononitrile, cyanoacetophenone, cyanothioacetamide and ethylcyanoacetate to give the corresponding pyrrolo[3,4–h]quinoline derivatives **4a–e**, **5a–e**, **6a–e** and **7a–e** respectively. The structure of the newly synthesized compounds was established on the basis of elemental analysis and spectral data studies.

Key words: Substituted furan, N-Arylmaleimides, Cyanoacetophenone, Malononitrile,Cyanothioacetamide, Ethylcyanoacetate, and N–Arylphthalimides derivatives.

Introduction

Maleimides are an important class of substrates for biological and chemical applications. They are used as chemical probes of protein structure[1], immunoconjugates for cancer therapy, solid supported enzymes for synthetic applications, haptene for the production of antibodies[2] or new herbicides and pesticides[3]. Some compounds of the dicarboxyimide type are reported to reveal effective system activity against Botrytis cinerea, Cochliobolus miyabeanus and Pellicularia sasaci [3]. N-(3,5-Dichlorophenyl)pyrrolidine-2,5-dione (Dimetachlon) is being used as a protective and curative fungicide[4] and the cycloadducts of N-(3,5-dichlorophenyl) maleimide to furan[5] and its derivatives have also considerable fungicidal properties. The maleimide moiety can be used as a platform in synthesis due to its Michael accepting ability, dienophilic nature[6, 7] as well as to its reactivity as a dipolarophile in 1,3 and 1,4-dipolar cycloadditions[8-16]. The divers biological activities of compounds containing the (-CONHCO-) and (-CONRCO-) moieties as very effective and persistent foliage fungicides especially for control of apple and pear scab and also as seed dressings against many soil and seed-born disease[17, 18] stimulated our interest for synthesis of several new derivatives of these ring systems for biological activity studies, as a part of our program[9-11, 18-25] directed for the synthesis of new heterocyclic compounds.

Results and Discussion:

We report, here, new methods for synthesis of some phthalimide derivatives and some pyrrolo[3,4–h] quinoline derivatives.

Thus, it has been found that 2-amino-3-cyano-4-ethoxycarbonyl-5-methyl furan **1** reacted with N-arylmaleimides **2a–e** in xylene to afford the fully substituted N-arylphthalimide derivatives **3a–e** (cf. scheme 1).The structures of **3a-e** were established based on the data of IR, ^{1}H-NMR spectra and elemental analysis (cf. Table 1 and 2).

The IR spectra of these compounds showed a band of NH_2, a band of CN, a band of ester group and two separated bands attributed to the presence of CO-NAr-CO groups[26] in each case. While their ^{1}H-NMR spectra revealed the signals of -$\underline{CH_2}CH_3$, -$CH_2\underline{CH_3}$, $\underline{CH_3}$- Ar and aromatic protons, moreover the mass spectra of **3a-b**, and **3d** as typical examples gave m/z = 363, 399 and 367 which corresponded to the molecular formula $C_{20}H_{17}N_3O_4$, $C_{23}H_{17}N_3O_4$ and $C_{19}H_{14}N_3O_4F$ respectively.

Synthons **3a-e** are used as the starting material for the synthesis of many pyrrolo [3,4 -h] quinoline derivatives. Thus it has been found that compounds **3a–e** reacted with malononitrile to give the fully substituted pyrrolo [3, 4 -h] quinoline derivatives **4a-e**. The structures of the reaction products 4a-e were confirmed based on the data of IR, ^{1}H-NMR spectra and elemental analysis. (cf. Table 1 and 2)

The synthetic potential of **3a-e** was further directed toward the synthesis of other pyrrolo[3,4 -h] quinoline derivatives through their reaction with cyanoac etophenone, cyanothioacetamide and ethylcyanoacetate in presence of piperidine to give the corresponding pyrrolo[3,4-h]quinoline derivative **5-7a-e** respectively. The structures of the products were established based on the data given from elemental analysis, IR, and ^{1}H-NMR spectra studies (cf. Table 1 and 2).

Experimental:

All melting points are uncorrected. The IR spectra in KBr discs were recorded on pye-Unicam SP-1000 spectrophotometer. The ^{1}H-NMR spectra were recorded on Varian Em 390-90 MHz Gem 200 and Bruker WP-80 spectrometers using $(CD_3)_2SO$ as solvents and TMS as an internal standard. Chemical shifts are expressed as δ ppm unit. Mass spectra were recorded on a Hewlett-Packard- GC-Ms type 2988 series using DIP technique at 70 ev. Micro analysis was performed at the Micro analytical center, Cairo University using a Perkin-Elemer 2400 CHN elemental analyzer.

Preparation of N-arylphthalimides 3a– e:

General procedure: Reaction of 2-amino-3-cyano-4-ethoxycarbonyl-5-methyl furan **1** (0.01 mole) with each of N-(benzyl, α-naphthyl, β-naphthyl, p-fluorophenyl, and p-bromophenyl) maleimides **2a–e** (0.01 mole). The elimination of water in reaction of 1 and 2a-e occurs by reflux in xylene (50 ml) for 5 hours. The solid products **3a-e** were obtained from hot solution. After cooling the products were

filtered off and recrystallized from proper solvent (at boiling point of the solvent) or after concentration and cooling (cf. Table 1 and 2).

3a as yellow crystals m.p. 173 °C, yield 80 %; **3b** as brown crystals with m.p. 180 °C, yield 70 %; **3c** as brown crystals with m.p. 183 °C, yield 75 %; **3d** as yellow crystals m.p. 170 °C, yield 80 %; **3e** as brown crystals with m.p. 176 °C, yield 76 %.

Reactions of N-arylphthalimides 3a-e with malononitrile, cyanoace- tophenone, and cyanothioacetamide:

General procedure: A mixture of each of the N-arylphthalimides **3a–e** (0.01 mole) and each of malononitrile, cyanoacetophenone, or cyanothioacetamide (0.01 mole) in absolute ethanol (40 ml) in the presence of piperidine (0.5 ml) was heated under reflux for 6 hours. The solid products **4a-e, 5a-e** and **6a-e** obtained from hot solution after cooling were filtered off and recrystallized from proper solvent (at boiling point of the solvent) or after concentration and cooling (cf. Table 1and 2).

4a as yellow crystals m.p. > 300 °C, yield 75 %; **4b** as brown crystals with m.p. >300 °C, yield 70 %; **4c** as brown crystals with m.p. >300 °C, yield 70 %; **4d** as yellow crystals with m.p. >300 °C, yield 75 %; **4e** as brown crystals with m.p. >300 °C, yield 80 %.

5a as brown crystals with m.p. >300 °C, yield 70 %; **5b** as brown crystals with m.p. >300 °C, yield 75 %; **5c** as brown crystals with m.p. >300 °C, yield 73%; **5d** as brown crystals with m.p. >300 °C, yield 75 %; **5e** as brown crystals with m.p. >300 °C, yield 74 %.

6a as yellow crystals m.p. > 300 °C, yield 80 %; **6b** as yellow crystals m.p. > 300°C, yield 75 %; **6c** as yellow crystals m.p. > 300°C, yield 75 %; **6d** as yellow crystals m.p. > 300°C, yield 70 %; **6e** as yellow crystals m.p. > 300°C, yield 74 %.

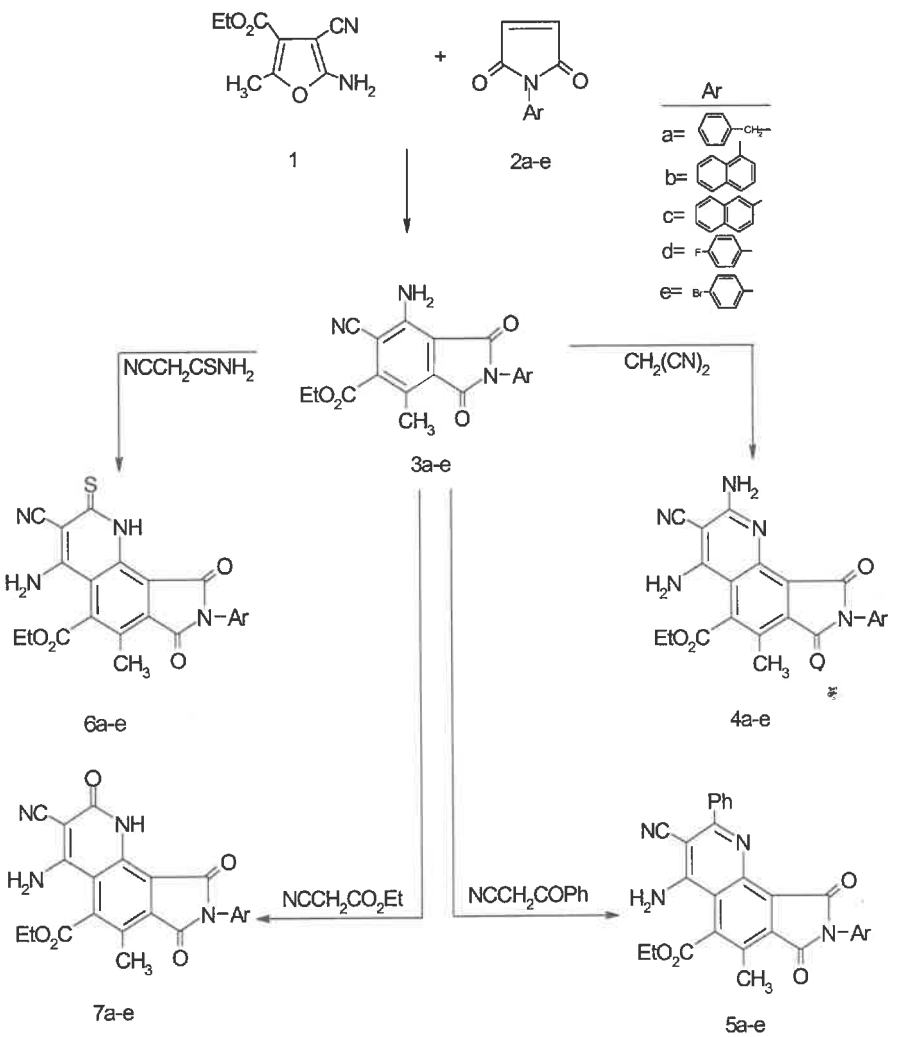
Reactions of N-arylphthalimides 3a–e with ethyl cyanoacetate:

A solution of each of the N-arylphthalimides **3a–e** (0.01 mole) in ethyl cyanoacetate (30 ml) in the presence of piperidine (0.5 ml) was heated under reflux for 5 hours. The solid products **7a-e** obtained from hot solution after cooling filtered off and recrystallized from proper solvent (at boiling point of the solvent) or after concentration and cooling (cf. Table 1 and 2).

7a as yellow crystals m.p. > 300°C, yield 70 %; **7b** as yellow crystals m.p. > 300°C, yield 70 %; **7c** as brown crystals with m.p. >300 °C, yield 75 %; **7d** as brown crystals with m.p. >300 °C, yield 80 %; 7e as brown crystals with m.p. >300 °C, yield 75 % .

Conclusions:

Application of 1, 4- Dipolarcycloaddation reaction in synthesis of same organic adducts and some maleimides which are important class of substrates for biological and chemical applications


EtO2C
CN
H3C
O
NH2
1
+
O
N
O
Ar
2a-e
Ar
a=
b=
c=
d=
e=
NH2
NC
O
N–Ar
EtO2C
CH3
O
3a-e
NCCH2CSNH2
CH2(CN)2
S
NH
6a-e
4a-e
NCCH2CO2Et
NCCH2COPh
7a-e
Ph
5a-e

(Scheme - 1)

Table (1):- Characterization data of the newly synthesized derivatives.

Comp. No	Molecular Formula	Color / Yield %	M. P °C/ Cryst. Solvent	% of Analysis, Calcd. / Found				
				C	H	N	S	X
3 a	$C_{20}H_{17}N_3O_4$	yellow 80	173 EtOH	66.11 66.10	4.68 4.62	11.57 11.55	–	–
3 b	$C_{23}H_{17}N_3O_4$	Brown 70	180 EtOH	69.17 69.20	4.26 4.28	10.52 10.55	–	–
3 c	$C_{23}H_{17}N_3O_4$	Brown 75	183 EtOH	69.17 69.25	4.26 4.24	10.52 10.53	–	–
3 d	$C_{19}H_{14}N_3O_4F$	yellow 80	170 AcOH	62.12 62.13	3.81 3.72	11.44 11.42	–	F, 5.17 5.22
3 e	$C_{19}H_{14}N_3O_4Br$	Brown 76	176 AcOH	53.27 53.10	3.27 3.20	9.81 9.78	–	Br, 18.69 18.54
4 a	$C_{23}H_{19}N_5O_4$	yellow 75	> 300 EtOH	64.33 64.32	4.42 4.42	16.31 16.23	–	–
4 b	$C_{26}H_{19}N_5O_4$	Brown 70	> 300 EtOH	67.09 67.11	4.08 4.21	15.05 15.03	–	–
4 c	$C_{26}H_{19}N_5O_4$	Brown 70	>300 EtOH	67.09 67.00	4.08 4.21	15.05 15.02	–	–
4 d	$C_{22}H_{16}N_5O_4F$	yellow 75	> 300 Ac OH	60.96 60.82	3.69 3.66	16.16 16.11	–	F, 4.38 4.32
4 e	$C_{22}H_{16}N_5O_4Br$	Brown 80	> 300 Ac OH	53.44 53.45	3.23 3.02	14.17 14.01	–	Br, 16.19 16.10
5 a	$C_{29}H_{22}N_4O_4$	Brown 70	> 300 EtOH	71.02 71.04	4.48 4.38	11.42 11.22	–	–
5 b	$C_{32}H_{22}N_4O_4$	Brown 75	> 300 EtOH	73.00 73.12	4.18 4.21	10.64 10.70	–	–
5 c	$C_{32}H_{22}N_4O_4$	Brown 73	> 300 EtOH	73.00 73.10	4.18 4.19	10.64 10.69	–	–
5 d	$C_{28}H_{19}N_4O_4F$	Brown 75	> 300 EtOH	68.01 68.00	3.84 3.72	11.33 11.23	–	F, 3.84 3.81
5 e	$C_{28}H_{19}N_4O_4Br$	Brown 74	> 300 EtOH	60.54 60.50	3.42 3.33	10.09 10.02	–	Br, 14.41 14.32

6 a	$C_{23}H_{18}N_4O_4S$	yellow 80	> 300 AcOH	61.88 61.78	4.03 4.05	12.55 12.33	7.17 7.02	–
6b	$C_{26}H_{18}N_4O_4S$	yellow 75	> 300 AcOH	64.73 64.75	3.73 3.78	11.61 11.65	6.63 6.66	–
6c	$C_{26}H_{18}N_4O_4S$	yellow 75	> 300 AcOH	64.73 64.77	3.73 3.75	11.61 11.67	6.63 6.68	–
6 d	$C_{22}H_{15}N_4O_4SF$	yellow 70	> 300 AcOH	58.66 58.55	3.33 3.11	12.44 12.21	7.11 7.00	F, 4.22 4.00
6 e	$C_{22}H_{15}N_4O_4SBr$	yellow 74	> 300 AcOH	51.66 51.54	2.93 2.83	10.95 10.82	6.26 6.33	Br, 15.65 15.52
7 a	$C_{23}H_{18}N_4O_5$	yellow 70	> 300 AcOH	64.18 64.12	4.18 4.33	13.02 13.00	–	–
7 b	$C_{26}H_{18}N_4O_5$	yellow 70	> 300 AcOH	66.95 66.85	3.86 3.75	12.01 12.11	–	–
7 c	$C_{26}H_{18}N_4O_5$	Brown 75	> 300 AcOH	66.95 66.71	3.86 3.95	12.01 12.02	–	–
7 d	$C_{22}H_{15}N_4O_5F$	Brown 80	> 300 AcOH	60.82 60.80	3.45 3.33	12.90 12.82	–	F, 4.37 4.23
7 e	$C_{22}H_{15}N_4O_5Br$	Brown 75	> 300 AcOH	53.33 53.21	3.03 3.06	11.31 11.22	–	Br,16.16 16.26

Table (2):- IR (cm^{-1}) and ^{1}H-NMR δ (ppm) data

Comp	IR (cm^{-1})	^{1}H-NMR δ (ppm)
3a	3400, 3320 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO).	1.3 (3H, t, -CH_2<u>CH_3</u>); 2.4 (3H, s, <u>CH_3</u>-Ar); 3.9 (2H, q, -<u>CH_2</u>CH_3); 4.1 (2H, s, N<u>CH_2</u>-Ph); 6.5 (2H, s, br, NH_2); 7.2-8.2 (5H, m, Ar H· s).
3c	3400, 3320 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO).	1.3 ((3H, t, -CH_2<u>CH_3</u>); 2.4 (3H, s, CH_3-Ar); 3.9 (2H, q, -<u>CH_2</u>CH_3); 6.4(2H, br, NH_2); 7.2-8.2 (7H, m, Ar H· s).
3d	3400, 3320 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO).	1.3 ((3H, t, -CH_2<u>CH_3</u>); 2.4 (3H, s, <u>CH_3</u>-Ar); 3.9 (2H, q, - <u>CH_2</u>CH_3); 6.5 (2H, br, NH_2); 7.2-8.0 (4H, m, Ar H· s)
4a	3400, 3320 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO).	1.2 (3H, t, -CH_2<u>CH_3</u>); 2.5 (3H, s, -<u>CH_3</u>-Ar); 4.0 (2H, q, - <u>CH_2</u>CH_3); 4.2 (2H, s, N<u>CH_2</u>-Ph); 7.0-8.2 (5H, m, Ar H· s); 9.5 (4H, br, two NH_2).
4c	3400, 3320 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO).	1.3 (3H, t, -CH_2<u>CH_3</u>); 2.6 (3H, s, <u>CH_3</u>-Ar); 3.9 (2H, q, -<u>CH_2</u>CH_3); 7.1-8.2 (7H, m, Ar H· s); 9.5 (4H, br, two NH_2).
4d	3400, 3320 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO).	1.2 (3H, t, -CH_2<u>CH_3</u>); 2.5 (3H, s, <u>CH_3</u>-Ar); 3.9 (2H, q, -<u>CH_2</u>CH_3); 7.1-8.1 (4H, m, Ar H· s); 9.4 (4H, br, two NH_2).
5a	3400, 3320 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO).	1.3 (3H, t, -CH_2<u>CH_3</u>); 2.4 (3H, s, <u>CH_3</u>-Ar); 3.8 (2H, q, -<u>CH_2</u> CH_3); 4.0 (2H, s, N<u>CH_2</u>-Ph); 7.2-8.0 (5H, m, ArH· s); 9.5 (2H, br, NH_2).
5c	3400, 3320 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO).	1.2 (3H, t, -CH_2<u>CH_3</u>); 2.4 (3H, s, <u>CH_3</u>-Ar); 3.8 (2H, q, -<u>CH_2</u>CH_3); 7.2-8.2 (12H, m, Ar H· s); 9.3 (2H, br, NH_2).
6a	3400, 3300 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (-CO NAr CO).	1.3 (3H, t, -CH_2<u>CH_3</u>); 2.5 (3H, s, <u>CH_3</u>-Ar); 3.9 (2H, q, -<u>CH_2</u>CH_3); 4.1(2H, s, N<u>CH_2</u>-Ph); 7.2-8.2 (5H, m, ArH· s and 1H, NH); 9.4 (2H, br, NH_2).
6c	3400, 3320 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (-CO NAr CO).	1.2 (3H, t, -CH_2<u>CH_3</u>); 2.4 (3H, s, <u>CH_3</u>-Ar); 4.0 (2H, q, -<u>CH_2</u>CH_3); 7.2-8.3(7H, m, Ar H· s and 1H, NH); 9.3 (2H, br, NH_2).
6d	3400, 3330 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO).	1.3 (3H, t, -CH_2<u>CH_3</u>); 2.4 (3H, s, <u>CH_3</u>-Ar); 4.0 (2H, q, -<u>CH_2</u>CH_3); 7.2-8.1 (4H, m, Ar H· s and 1H, NH); 9.5 (2H, br, NH_2).
7a	3400, 3330 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO), 1680 (CO amidic).	1.2 (3H, t, -CH_2 <u>CH_3</u>); 2.5 (3H, s, <u>CH_3</u>-Ar); 3.8 (2H, q, -<u>CH_2</u>CH_3); 4.1 (2H, s, N<u>CH_2</u>-Ph); 7.2-8.2 (5H, m, Ar H· s and 1H, NH); 9.6 (2H, br, NH_2).
7c	3400, 3330 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO), 1680 (CO amidic).	1.3 (3H, t, -CH_2<u>CH_3</u>); 2.4 (3H, s, <u>CH_3</u>-Ar); 4.0 (2H, q, -<u>CH_2</u>CH_3); 7.2-8.3 (7H, m, Ar H· s and 1H, NH); 9.4 (2H, br, NH_2).
7d	3400, 3330 (NH_2), 2200 (CN), 1730 (ester CO), 1790- 1720 and 1719-1690 (CO NAr CO), 1680 (CO amidic).	1.2 (3H, t, -CH_2<u>CH_3</u>); 2.5 (3H, s, <u>CH_3</u>-Ar); 3.9 (2H, q, -<u>CH_2</u>CH_3); 7.2-8.4 (4H, m, Ar H· s); 9.5 (2H, br, NH_2).

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