Preparation and Identification of some new Pyrazolopyrin derivatives and their Polymerizations study

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Abstract:

This work describes the synthesis and polymerization properties of some novel polysubstituted fused heterocyclic ring Systems namely; Pyrano [4, 3-C] Pyrazoles and pyrazolo [4, 3-C] Pyridines. Such targeted compounds where designed so as to hybridize the Pyrazole ring with the pyrone and/or pyridine moieties, respectively. The chemistry of the reactions employed in the synthesis of the target compounds together with their chemical behavior, are discussed and the structures of the newly synthesized compounds were confirmed by the IR and ¹H-NMR spectral data. A series of copolymers 1-(3,6-dimethyl-4-oxo-1,4-dihydro-5H-pyrazolo [4,3-C] pyridin-5-yl)-1H-pyrrole-2,5-Dione S₁, 1-[2-(3,6-dimethyl-4-oxo-1-phenyl-1, 4-dihydro-5Hpyrazolo [4,3-C] pyridin-5-yl)ethyl]-1H-pyrrole-2,5-Dione S₂ and 1-(3, 6-dimethyl-4oxo-1-phenyl-1,4-dihydro-5H-pyrazolo[4,3-C]pyridin-5-yl)-1H-pyrrole 2,5-Dione S₃ with Acrylic acid (AA) were prepared by free radical polymerization in absolute ethanol at 70C° using Benzoyl peroxide as initiator. The reactivity ratios of the monomers were determined by Fineman- Ross and Kelen-Tudos methods. Mean Sequence lengths of copolymers are estimated from r_1 and r_2 values. It shows that the AA unit increases in a linear fashion in the polymer chain as the concentration of AA increases in the monomer feed.

Key words: Synthesis; Fused Pyrazoles,1-(3,6-dimethyl-4-oxo-1,4-dihydro-5H-pyrazolo [4,3-C] pyridin-5-yl)-1H-pyrrole-2,5-Dione S₁, 1-[2-(3,6-dimethyl-4-oxo-1-phenyl-1,4-dihydro-5H-pyrazolo[4,3-C]pyridin-5-yl)ethyl]-1H-pyrrole-2,5-DioneS₂ and 1-(3,6-dimethyl-4-oxo-1-phenyl-1,4-dihydro-5H-pyrazolo[4,3-C]pyridin-5-yl)-1H-pyrrole-2,5-Dione S₃, reactivity ratios, copolymer composition, Mean Sequence lengths.

Introduction:

Among the wide variety of heterocycles that have been explored for developing potential pharmacologically active compounds, pyrazoles fused with different heterocycles that are known to contribute to various chemotherapeutic emerged effects have as antimicrobial, [1,2] antifungal, [3] and antiviral agents.[4] In addition, some pyrazole derivatives fused were reported induce various antileukemic, [5] antitumor [6, 7] and

antiproliferative [8, 9] activities. Motivated by these facts, we were interested to synthesize and investigate the in vitro anticancer, antibacterial and antifungal activities of some novel polysubstituted fused heterocyclic ring namely; pyrano systems [4,3 C]pyrazoles and pyrazolo [4,3-cC] pyridines. Such targeted compounds where designed so as to hybridize the pyrazole ring with the pyrone and/or pyridine moieties, respectively, hoping to obtain synergistic anticancer and/or

*Chemistry Department, College of Science, AL-Mustansiriyah University **Chemistry Department, College of Science for Women, Baghdad University antimicrobial activities. The structures of the newly synthesized compounds confirmed with elementary were microanalyses and substantiated with IR and 1H-NMR data. The chemical structure of a copolymer depends not only on the two-monomer units forming the macromolecule, but also on how such units are distributed along macromolecular chains. This distribution is a direct consequence of each monomer's reactivity in the copolymer molecule [10-13]. The determination copolymer of composition and reactivity ratios of the monomers is important in evaluating the specific application of the copolymer [14]. The monomer reactivity ratios determined by conventional linearization methods. The copolymer composition was determined by Kjeldahl analysis for the copolymer. Knowledge of the copolymer composition is an important step in the evaluation of its utility. Copolymer composition and monomer distribution in the copolymer are dependent on the reactivity ratios. The most common mathematical model of copolymerization is based on finding relationship the between the composition of copolymers and the composition of the monomer feed in which the monomer reactivity ratios are the parameters to be determined [15-18]. The accurate estimation of copolymer composition and determination of monomer reactivity ratios are significant for tailor-made copolymers with required physical and chemical properties and in evaluating the specific end application of the copolymers. The present article reports the synthesis and characterization of series of copolymers S_1 , S_2 and S_3 with Acrylic acid. The determination of monomer reactivity ratios of the monomers and mean sequence lengths of copolymers are also reported.

Materials and Methods:

Melting points were determined open glass capillaries on a in Gallenkamp Melting point apparatus. The infrared (IR) spectra were recorded on Shimadzu FT-IR 8400S infrared spectrophotometer using the KBr Plate technique. The 1H-NMR spectra were recorded on a Varian EM 360 spectrometer using tetramethylsilane internal as the standard and DMSO-d6 as the solvent (Chemical shifts in δ , ppm). Splitting patterns were designated as follows: S: Singlet; D: Doublet; M: Multiplet. Kjeldahl analyses were performed at the Laboratory College of Science University of the Baghdad.

Pyrazoles, 1-(3, 6-dimethyl-4-oxo-1,4-dihydro-5H-pyrazolo [4,3-C] pyridin-5-yl)-1H-pyrrole-2,5-Dione S_1 :

A solution of the appropriate 5-6-Dimethyl-2H-Pyridine-Amino-3. 4(5H) one (5gm, 0.0281mole) in Glacial acetic acid (25ml) was refluxed with Maleic anhydride (5.51gm 0.0562mole) for 14hr The reaction mixture was concentrated to half its volume and allowed to cool in ice bath. The solid product separated by filtration, washed thoroughly with water, dried and recrystallized from Physicochemical ethanol. and analytical data are recorded in Table 1. 1HNMR and IR spectra are shown in Table 2.

1-[2-(3, 6-dimethyl-4-oxo-1-phenyl-1,4-dihydro-5H-pyrazolo[4,3-C]pyridin-5-yl)ethyl]-1H-pyrrole-2,5-Dione S₂:

A solution of the appropriate 5-(2-aminoethyl)-3, 6-dimethyl-1phenyl-1, 5-dihydro-4H-pyrazolo [4, 3c] pyridine-4-one (5gm , 0.0177mole) in Glacial acetic acid (25ml) was refluxed with Maleic anhydride (3.47gm , 0.0354mole) for 14hr The reaction mixture was concentrated to half its volume and allowed to cool ice bath. The solid product separated by filtration, washed thoroughly with water, dried and recrystallized from ethanol. Physicochemical and analytical data are recorded in Table 1. 1HNMR and IR spectra are shown in Table 2.

1-(3, 6-dimethyl-4-oxo-1-phenyl-1,4dihydro-5H-pyrazolo[4,3-C]pyridin-5-yl)-1H-pyrrole-2,5-Dione S₃:

A solution of the appropriate 5amino-3, 6-dimethyl-1-phenyl-1, 5dihydro-4H-pyrazolo [4, 3-c] pyridine-4-one (5gm, 0.0197mole) in Glacial acetic acid (25ml) was refluxed with anhydride Maleic (3.86gm 0.0394mole) for 14hr The reaction mixture was concentrated to half its volume and allowed to cool ice bath. The solid product separated bv filtration, washed thoroughly with water, dried and recrystallized from ethanol. Physicochemical and analytical data are recorded in Table 1. 1HNMR and IR spectra are shown in Table 2.

Acrylic acid was washed with water and dried over anhydrous CaCl2. The Acrylic acid was then distilled in an atmosphere of Nitrogen under reduced pressure. The clean and dried Acrylic acid stored in bottle and kept in the refrigerator at 5° C. Benzoyl proxide (BPO) was recrystallized from chloroform. Diethyl ether was dried with Megnesium Sulphate All the solvents were purified by distillation prior to their use. The Comonomers of series of S_1 , S_2 , S_3 was purified by

washing successively with 5% NaOH and distilled water, dried, and finally distilled at reduced pressure under nitrogen at 60 °C.

Copolymerization

A total feed of 5 gm of series monomers S_1 , S_2 and S_3 with Acrylic acid and 0.1gm of BPO initiator were dissolved in 8ml of ethanol placed in a standard reaction tube to obtain a homogenous solution. The mixture was flushed with oxygen free dry nitrogen gas. The reaction tubes then immersed in a thermostatic water bath maintained at 70°C. The copolymerization reaction was allowed to proceed for an appropriate duration that would give a conversion below 10%. Then cooled to R.T. The solution poured in petroleum ether to precipitate the copolymer. The copolymer washed with petroleum ether and dried in vacuum oven for 24 hours.

Instrumentation

The 1H-NMR spectra of monomers were recorded on the Bruker DMX-500 NMR Spectrophotometer operating at 300-600 MHz respectively DMSO-d6 as the solvent.

Results and Discussion: Copolymerization

A series of copolymers S_1 , S_2 and S_3 with Acrylic acid were prepared by free radical polymerization in ethanol at 70 °C using BPO as initiator. The schematic representation of the copolymer is given bellow:



Fig. 1: Copolymerization of S1, S2 and S3 with Acrylic acid

Determination of copolymer composition

The copolymer composition was determined by Kjeldahl analysis for the copolymer.

Reactivity ratios

The monomer feed ratios and the resultant copolymer compositions, the reactivity ratios of monomers 1 (S_1 , S_2 , S_3) and monomer 2 (AA) were evaluated by the methods of Fineman-Ross (F-R) and Kelen- Tudos (K-T). The significant parameters of F-R and K-T and equation are presented in Table 3,7,11 and Table 4.8.12 respectively. The reactivity ratios for S_1 , S_2 , S_3 (r_1) and AA (r_2) from the F-R plot (Figure 2) and K-T plot are given in Table 5,9,13 and (Figure 3). The value(S) of r_1 is less than 1 and r_2 is greater than 1. The r_1 shows that S_1 , S_2 , S₃ favors cross-propagation as opposed to homopropagation and r_2 shows that AA favors homopropagation over cross-propagation. The r_1 and r_2 together show that AA is generally more reactive than S_1 , S_2 , S_3 , hence the copolymers contain a higher proportion of AA units.

Mean sequence length

The mean sequence length was determined using the pertinent equations:

$$\mu_{1} = r_{1} \frac{M_{1}}{M_{2}} + 1 \qquad (1)$$

$$\mu_{2} = r_{2} \frac{M_{2}}{M_{1}} + 1 \qquad (2)$$

 $[M_1]$ represent the concentration of S_1 , S_2 or S_3 and $[M_2]$ AA, in the monomer feed. The mean sequence lengths of copolymers are given in Table 6, 10, 14. It is significant to note that from the Table 6, 10, 14 the AA units'

increases in a linear fashion in the polymer chain as the concentration of AA increases in the monomer feed.

Table1. Physicochemical andanalytical data for compounds 1-3.

Cpd No.	R	Yield (%)	M.p. (*C)	Mol. Form.
S ₁	-	93.56	80-82	$C_{12}H_{10}N_4O_3$
S_2	C ₆ H ₅	83.59	76-78	$C_{20}H_{18}N_4O_3$
S ₃	C ₆ H ₅	85.7	140-142	$C_{18}H_{14}N_4O_3$

Table2. ¹H-NMR(δ -ppm) and IR(Cm⁻¹) spectra of some1-3.

Cpd	CH ₃ (S, 3H)	H-6 (S, 1H)	IR (Cm ⁻¹)
S_1	-	-	1716.65(CO), 3414(NH)
S_2	1.789,2.657	6.099	1716.65(CO)
S_3	3.023,3.054	5.552	1716.65(CO)

Table3: Fineman-Ross	parameters for the	e Copolymerization	of $S_1 - C_0 - AA$
	pur unice of bron ene		

Mole fraction of S ₁ in feed,M ₁	Mole fraction of AA in feed, M ₂	fraction of S ₁ in copolymer, m ₁	Mole fraction of AA in copolymer, m ₂	F=M ₁ /M ₂	F=m ₁ /m ₂	(F-1) /f	F /f ²
0.2	0.8	0.003824	0.015496	0.250	0.2468	-3.3666	2.8560
0.3	0.7	0.004391	0.010309	0.429	0.4259	-1.7283	1.4548
0.4	0.6	0.006016	0.009072	0.667	0.6631	-1.0131	0.7464
0.5	0.5	0.007552	0.007958	1.000	0.9489	-0.3764	0.7139
0.6	0.4	0.009063	0.006135	1.500	1.4771	-0.0822	0.4027
0.7	0.3	0.010578	0.004581	2.333	2.3091	0.2008	0.2745
0.8	0.2	0.012087	0.003082	4.000	3.9213	0.2024	0.1167

Table4: kelen-Tudos parameters for the Copolymerization of $S_1 - C_0 - AA$

the cope			
G = F(f-1)	H =F2 /	N =G /(α +	$A = H / (\alpha$
/ f	f	H)	+ H)
-1.1791	0.3501	-0.5662	0.1681
-1.1871	0.6874	-0.4906	0.2841
-1.3573	1.3397	-0.4418	0.4361
-0.5273	1.4007	-0.1683	0.4518
-0.2041	2.4833	-0.0484	0.5891
0.7315	3.6428	0.1361	0.6777
1.7351	8.5726	0.1684	0.8319
4 = 2 4 4			

α= 1.7324

Table5.Copolymerizationparameter, for the Copolymerizationof $S_1 - Co - AA$

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Methods	\mathbf{r}_1	\mathbf{r}_2	r ₁ . r ₂
Fineman-Ross (F-R)	0.38	1.35	0.513
Kelen-Tudos (K-T)	0.30	1.42	0.426

Table6. Mean Sequence Lengths in Copolymerization of $S_1 - C_0 - AA$

AA in feed, M ₂ (Mole %)	μ'1	μ'2	μ' ₁ : μ'2	Distribution
0.80	1.0587	9.0014	1:9	SA ₉ S
0.70	1.0897	6.2292	1:6	SA ₆ S
0.60	1.1116	5.2047	1:5	SA_5S
0.50	1.2186	3.1467	1:3	SAAAS
0.40	1.2987	2.5706	1:2	SAAS
0.30	1.4977	1.9428	1:2	SAAS
0.20	1.6099	1.7694	2:2	SSAASS

 $r_1 = 0.38$; $r_2 = 1.35$

Only a few cases are illustrated (S = S₁; A=AA)



Fig.2: Fineman-Ross (F-R) plot

Fig. 3: kelen-Tudos (K-T) plot

Fineman-Ross	parameters for th	e Copol	ymerization o	of $S_2 - Co - AA$
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Mole fraction	Mole fraction	Fraction of S_2	Mole fraction of				
of S ₂ in	of AA in	in	AA in	$F=M_1/M_2$	$F=m_1/m_2$	(F-1) /f	F /f ²
feed M.	feed,	copolymer,	copolymer,				
iccu,m1	M_2	m ₁	m ₂				
0.2	0.8	0.002428	0.009735	0.250	0.2494	-3.4844	2.1061
0.3	0.7	0.003127	0.007306	0.429	0.4280	-1.7888	1.2795
0.4	0.6	0.004297	0.006450	0.667	0.6662	-1.1396	0.8131
0.5	0.5	0.005256	0.005279	1.000	0.9956	-0.5803	0.4261
0.6	0.4	0.006545	0.004367	1.500	1.4987	-0.1779	0.3264
0.7	0.3	0.007495	0.003216	2.333	2.3305	0.0195	0.1926
0.8	0.2	0.008285	0.002076	4.000	3.9908	0.1033	0.0887

Table8: kelen-Tudos parameters for the Copolymerization of S₂ – Co – AA

$\mathbf{G} = \mathbf{F}(\mathbf{f-1}) / \mathbf{f}$	H = F2 / f	$N = G / (\alpha + H)$	$\mathbf{A} = \mathbf{H} / (\boldsymbol{\alpha} + \mathbf{H})$
-1.6544	0.4748	-0.5933	0.1703
-1.3979	0.7816	-0.4516	0.2525
-1.4017	1.230	-0.3955	0.3471
-1.3620	2.3471	-0.2922	0.5036
-0.5449	3.0638	-0.1013	0.5697
0.1012	5.1931	0.0135	0.6918
1.1642	11.2749	0.0857	0.8297

α=2.3137

Table9. Copolymerization parameter, for the Copolymerization of S₂ – Co – AA

Methods	r ₁	\mathbf{r}_2	r ₁ . r ₂
Fineman-Ross (F-R)	0.31	1.77	0.5478
Kelen-Tudos (K-T)	0.3	1.7376	0.5213

Table10. Mean Sequence Lengths in Copolymerization of S₂ - Co - AA

AA in feed, M ₂ (Mole %)	μ'1	μ'2	μ' ₁ : μ' ₂	Distribution
0.80	1.0310	14.3623	1:14	SA ₁₄ S
0.70	1.0715	8.4653	1:8	SA ₈ S
0.60	1.0926	6.7640	1:6	SA ₆ S
0.50	1.1288	5.1442	1:5	SA ₅ S
0.40	1.2237	3.3861	1:3	SAAAS
0.30	1.3188	2.6741	1:3	SAAAS
0.20	1.4307	2.2394	1:2	SAAS

 $r_1 = 0.31$; $r_2 = 1.77$

Only a few cases are illustrated (S = S_2 ; A=AA)



Table11: Fineman-Ross parameters for the Copolymerization of S₃ – Co – AA

Mole fraction of S ₃ in feed,M ₁	Mole fraction of AA in feed, M ₂	fraction of S_3 in copolymer, m_1	Mole fraction of AA in copolymer, m ₂	F=M ₁ /M ₂	F=m ₁ /m ₂	(F-1) /f	F /f ²
0.2	0.8	0.002363	0.009517	0.250	0.2483	-3.3645	2.6677
0.3	0.7	0.003466	0.008101	0.429	0.4278	-1.7623	1.3448
0.4	0.6	0.004736	0.007118	0.667	0.6654	-1.0110	0.7262
0.5	0.5	0.005687	0.005734	1.000	0.9918	-0.5597	0.4521
0.6	0.4	0.006704	0.004493	1.500	1.4921	-0.1885	0.3229
0.7	0.3	0.008076	0.003479	2.333	2.3214	0.1588	0.2540
0.8	0.2	0.009019	0.002273	4.000	3.9679	0.2714	0.1319

Table12: kelen-Tudos parameters for the Copolymerization of S₃ – Co – AA

H = F2 / f	$N = G / (\alpha + H)$	$\mathbf{A} = \mathbf{H} / (\boldsymbol{\alpha} + \mathbf{H})$			
0.3748	-0.6117	0.1819			
0.7436	-0.5395	0.3061			
1.3771	-0.4587	0.4497			
2.2121	-0.3179	0.5676			
3.0965	-0.1220	0.6475			
3.9372	0.1266	0.7975			
7.5799	0.2220	0.8181			
	H =F2 / f 0.3748 0.7436 1.3771 2.2121 3.0965 3.9372 7.5799	H =F2 / fN =G /(α + H)0.3748-0.61170.7436-0.53951.3771-0.45872.2121-0.31793.0965-0.12203.93720.12667.57990.2220			

 $\alpha = 1.6855$

Table13. Copolymerization parameter, for the Copolymerization of S_3 – Co – AA

Methods	r	r ₂	r ₁ . r ₂
Fineman-Ross (F-R)	0.27	1.41	0.3807
Kelen-Tudos (K-T)	0.24	1.6026	0.3846

Table14. Mean Sequence Lengths in Copolymerization of S₃ - Co - AA

AA in feed, M ₂ (Mole %)	μ'1	μ'2	μ' ₁ : μ' ₂	Distribution
0.80	1.0420	10.1460	1:10	SA ₁₀ S
0.70	1.0628	7.1153	1:7	SA ₇ S
0.60	1.0820	5.6836	1:6	SA ₆ S
0.50	1.1134	4.3861	1:4	SAAAAS
0.40	1.1833	3.0938	1:3	SAAAS
0.30	1.3490	2.0997	1:2	SAAS
0.20	1.5296	1.7247	2:2	SSAASS

 $r_1=0.27$; $r_2=1.41$

Only a few cases are illustrated (S = S₃; A=AA)



Fig. 4: Fineman-Ross (F-R) plot

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Fig. 3: kelen-Tudos (K-T) plot

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تحضير و تشخيص بعض مشتقات البايراز ولوبايرين الجديدة و بلمرتها

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الخلاصة:

هذا البحث يصف تحضير وتشخيص و بلمرة بعض المركبات الحلقية غير المتجانسة المدمجة وهي؛ Pyrazoles [Pyrazoles [4,3-C] Pyrazoles [4,3-4,3-C] Pyrazoles . مثل هذه المركبات تُعين لتهجين حلقة البيرازول مع البيرون و / أو أصناف بيريدين، على التوالي. التفاعلات الكيميائية المستخدمة في تحضير المركبات تصف جنبا إلى جنب السلوك الكيميائي، مناقشة و تشخيص تركيب المركبات المحضرة في تحضير المركبات تصف جنبا إلى جنب السلوك الكيميائي، مناقشة و تشخيص تركيب المركبات المحضرة بوساطة IR و IR-NMR المعلومات الطيفية. السلاسل البوليمرية-1,4-0xolo [4,3-6] بوساطة IR و IR-NMR المعلومات الطيفية. السلاسل البوليمرية-1,4-0xolo [4,3-6] في تحضير المركبات تصف جنبا إلى جنب السلوك الكيميائي، مناقشة و تشخيص تركيب المركبات المحضرة بوساطة IR و IR-NMR المعلومات الطيفية. السلاسل البوليمرية-1,4-0xolo [4,3-6] في النهام-5H-pyrazolo [4,3-6] pyridin-5-yl)-1H-pyrrole-2,5-Dione S₁, 1-[2-(3,6dimethyl-4-oxo-1-phenyl-1, 4-dihydro-5H-pyrazolo [4,3-6] pyridin-5-yl)ethyl]-1Hpyrrole-2,5-Dione S₂ and 1-(3,6-dimethyl-4-oxo-1-phenyl-1,4-dihydro-5Hpyrazolo] وحامض الاكريليك (AA) تحضر بطريقة البلمرة بالجذور الحرة في أيثانول المطلق في °70C بأستخدام بيروكسيد البنزويل بوصفه كبادئ. نسب فعالية المونومرات تحدد بطريقة فاينمان- روس و كالين- تودس. يُقدر معدل طول الوحدات المتكررة للمونومر الواحد في سلسلة البوليمر المشترك من خلال قيم ₁, ₁, ₁ فإنه يدل على أن وحدة AA تزداد بطريقة خطية في سلسلة البوليمر و زيادة تركيز المونومر AA في مزيج التغذية.