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Synthesis of Pyrazoleacrylic Acids and Their Derivatives

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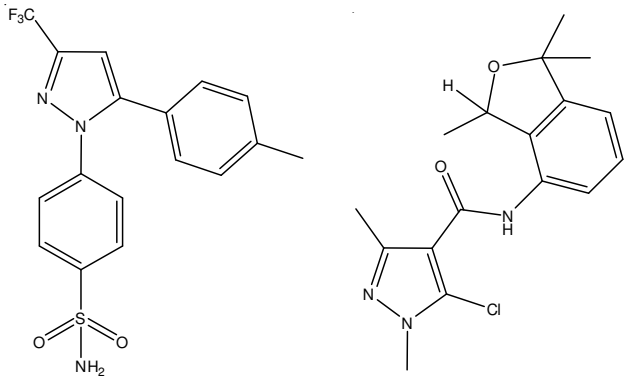
Various pyrazole acrylic acid derivatives were obtained by the Knoevenagel condensation of pyrazole-4-carbaldehydes with 'active methylene' compounds. In the condensation reaction with malonic acid and cyanoacetic acid, decarboxylation of the resulting acids was not observed. The products were characterized through spectroscopic techniques and elemental analysis.

Key Words: Pyrazoles, Knoevenagel condensation, Pyrazole-4-carbaldehydes.

INTRODUCTION

Knoevenagel condensation[1] is a very effective way of extending carbon chains and often exploited for the purpose. Pyrazole chemistry has afforded some interesting biological materials; one of these is COX-2 inhibitor *i.e.*, celecoxib[2] (a), already in clinical use, other is a well known agrochemical *i.e.*, furamtpyr[3] (b), used as a fungicide. In another azole researches such as with pyrrole some interesting pyrrole-3-acetic acid derivatives are being explored as NSAIDs[4]. Similar acid derivatives could easily be obtained from pyrazole-4-carbaldehydes.



(a) Celecoxib (b) Furamptyr

Fig. 1. Important pyrazole containing biological compounds

An appropriate pyrazolecarbaldehyde through Knoevenagel condensation could provide such a scaffold for posterior manipulation. Pyrazole-4-carbaldehydes are readily obtainable from various reactions such as: by the Rosenmund reduction of pyrazole-4-carbonyl chloride[5a,b], by the Sommelet reaction of the corresponding 4-chloromethylpyrazole[5c], by the Vilsmeier-Haack reaction of pyrazoles[6-9] or by the reaction of appropriate semicarbazones or hydrazones with Vilsmeier reagent[10,11]. Recently, a review on 1,3-diarylpyrazol-4-carbaldehyde has appeared in literature[12]. Some of these aldehydes have previously been condensed with various substrates such as acetophenones[7,13], 4-acetylpyrazole[14], pyruvic acid[15], hippuric acid[16], malonic acid[7,17], indole-3-acetonitrile[18] and benzopyrillium salts[19].

These considerations prompt us to continue our work on pyrazole chemistry and we have already reported some of our work on pyrazole derivatives[20]. Now we would like to present our results of Knoevenagel condensations of some pyrazole-4-carbaldehydes.

EXPERIMENTAL

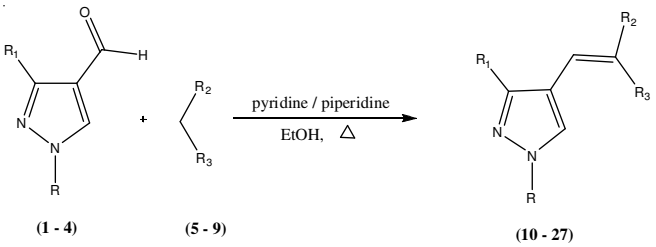
All the chemicals were purchased from Aldrich and used without further purification. The ^{1}H NMR spectra were taken on a Hitachi Perkin-Elmer spectrometer model R-20B operating at 60MHz (tetramethylsilane as internal reference). The IR absorption spectra were recorded as potassium bromide discs on a Perkin-Elmer model 180 spectrophotometer. Elemental

analysis was carried out on a Perkin-Elmer model 240. Melting points were obtained on a Fisher-Johns apparatus and are uncorrected.

Pyrazole-4-carbaldehydes: The following starting materials were prepared according to the literature methods: 1-Phenylpyrazole-4-carbaldehyde[21] (**1**): m.p. 76-78 ºC, yield 85 %. 1-*p*-Methoxyphenylpyrazole-4-carbaldehyde[22] (**2**): m.p. 83-84 ºC, yield 89 %. 3-Phenylpyrazole-4-carbaldehyde[11] (**3**): m.p. 128-129 ºC, yield 87 %. 1-*p*-Nitrophenylpyrazole-4-carbaldehyde[23] (**4**): m.p. 167-168 ºC, yield 78 %.

Knoevenagal condensations

General procedure: A mixture of 0.01 mol of the aldehyde, 0.01 mol of the "active methylene" compound, three drops of piperidine and five drops of pyridine in 10 mL of ethanol was heated under reflux for the required time as monitored by TLC. The reaction mixture was cooled and inverted over crushed ice, acidified with hydrochloric acid (pH 6), filtered, washed with cold water and dried. The dried precipitates were crystallized from an appropriate solvent. The following products (**Scheme-I**). were synthesized: 2-((1-Phenyl-1*H*-pyrazol-4-yl)methylene)malonic acid (**10**): m.p. 206-207 ºC, yield 1.93 g; 75 %. 2-((1-(4-Methoxyphenyl)-1*H*-pyrazol-4-yl)-methylene)malonic acid (**11**): m.p. 165-166 ºC, yield 2.12 g; 74 %. 2-((3-Phenyl-1*H*-pyrazol-4-yl)methylene)malonic acid (**12**): m.p. 169 ºC, yield 1.93 g; 75 %. 2-((1-(4-Nitrophenyl)-1*H*-pyrazol-4-yl)methylene)malonic acid (**13**): m.p. 204-206 ºC, yield 2.02 g; 67 %. Diethyl 2-((1-phenyl-1*H*-pyrazol-4-yl)methylene)malonate (**14**)[24]: m.p. 57-58 ºC, yield 2.34 g; 75 %. Diethyl 2-((1-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)methylene)malonate (**15**): m.p. 74-75 ºC, yield 2.43 g; 71 %. Diethyl 2-((1-(4-nitrophenyl)-1*H*-pyrazol-4-yl)methylene)-malonate (**16**): m.p. 128-129 ºC, yield; 2.47 g; 69 %. (Z)-2-Phenyl-3-(1-phenyl-1*H*-pyrazol-4-yl)acrylonitrile (**17**): m.p. 121-122 ºC, yield 1.63 g; 57 %. (Z)-3-(1-(4-Methoxyphenyl)-1*H*-pyrazol-4-yl)-2-phenylacrylonitrile (**18**): m.p. 169 ºC, yield 2.14 g; 68 %. (Z)-3-(1-(4-Nitrophenyl)-1*H*-pyrazol-4-yl)-2-phenylacrylonitrile (**19**): m.p. 276-278 ºC, yield 2.81 g; 85 %. (E)-Ethyl 2-cyano-3-(1-phenyl-1*H*-pyrazol-4-yl)acrylate (**20**): m.p. 132-133 ºC, yield; 2.20 g; 83 %. (E)-Ethyl 2-cyano-3-(1-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)acrylate (**21**): m.p. 151-152 ºC, yield 0.88 g; 30 %. (E)-Ethyl 2-cyano-3-(3-phenyl-1*H*-pyrazol-4-yl)acrylate (**22**): m.p. 167-168 ºC, yield 0.72 g; 27 %. (E)-Ethyl 2-cyano-3-(1-(4-nitrophenyl)-1*H*-pyrazol-4-yl)acrylate (**23**): m.p. 187-189 ºC, yield 0.87 g; 28 %. (E)-2-Cyano-3-(1-phenyl-1*H*-pyrazol-4-yl)acrylic acid (**24**): m.p. 212-214 ºC, yield 1.76 g; 74 %. (E)-2-Cyano-3-(1-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)acrylic acid (**25**): m.p. 236-238 ºC, yield 2.19 g; 82 %. (E)-2-Cyano-3-(3-phenyl-1*H*-pyrazol-4-yl)acrylic acid (**26**): m.p. 249 ºC, yield; 1.99 g; 84 %. (E)-2-Cyano-3-(1-(4-nitrophenyl)-1*H*-pyrazol-4-yl)acrylic acid (**27**): m.p. 320-322 ºC, yield; 2.26 g; 80 %. The results are presented in Tables 1 and 2.



(1 - 4) (5 - 9) (10 - 27)

R = H, Ph, p-MeOC$_6$H$_4$, p-NO$_2$C$_6$H$_4$; R$_1$ = H, Ph; R$_2$ = Ph, COOH, COOEt, CN; R$_3$ = COOH, COOEt, CN,

Scheme-I

RESULTS AND DISCUSSION

We had already reported the synthesis of various pyrazole-4-carbaldehydes and their derivatives[25]. The results of the present Knoevenagel condensations between the pyrazole-4-carboxaldehydes and the "active methylene" compounds are presented in **Scheme-I**. A mixture of pyridine and piperidine was used in these condensations[1]. The reactions were carried out in refluxing ethanol. The results are collected in Table-1. Table-2 contains the spectral data for the compounds obtained

TABLE-1
PHYSICAL DATA OF PRODUCTS[a]

Compd. No.	m.p. (ºC)	Solvents for crystallization	Yield (%)	m.f.	Elemental analysis (%): calcd. (found)		
					C	H	N
10	206-7	Chloroform	75	$C_{13}H_{10}N_2O_4$	60.46 (60.68)	3.90 (4.06)	10.85 (11.05)
11	165-6	Chloroform	74	$C_{14}H_{12}N_2O_5$	58.33 (57.97)	4.20 (4.36)	9.72 (9.34)
12	169	Acetic acid	75	$C_{13}H_{10}N_2O_4$	60.46 (60.11)	3.90 (3.73)	10.85 (10.47)
13	204-6	DMF[b]	67	$C_{13}H_9N_3O_6$	51.49 (51.56)	2.99 (2.94)	13.86 (14.22)
14	(57)[24]	Ethanol	75	$C_{17}H_{18}N_2O_4$	64.96 (65.05)	5.77 (5.81)	8.91 (8.72)
15	74-75	Ethanol	71	$C_{18}H_{20}N_2O_5$	62.73 (62.68)	5.85 (5.68)	8.14 (7.98)
16	128-9	Acetic acid	69	$C_{17}H_{17}N_3O_6$	56.82 (56.54)	4.77 (4.59)	11.69 (11.62)
17[c]	121-2	Ethanol	57	$C_{18}H_{13}N_3$	79.68 (79.44)	4.83 (4.73)	15.49 (15.23)
18[c]	169	Chloroform	68	$C_{19}H_{15}N_3O$	75.73 (75.58)	5.02 (5.07)	13.94 (13.88)
19[c]	276-8	Acetic acid	85	$C_{18}H_{12}N_4O_2$	68.35 (68.80)	3.82 (3.84)	17.71 (17.92)
20	132-3	Aq. Ethanol	83	$C_{15}H_{13}N_3O_2$	67.40 (67.18)	4.90 (4.80)	15.72 (15.87)
21	151-2	Ethanol	30	$C_{16}H_{15}N_3O_3$	64.64 (64.45)	5.08 (5.03)	14.13 (14.03)
22	167-8	Ethanol	27	$C_{15}H_{13}N_3O_2$	67.40 (67.52)	4.90 (4.84)	15.72 (16.00)
23	187-9	Ethanol	28	$C_{15}H_{12}N_4O_4$	57.69 (57.53)	3.87 (3.69)	17.94 (17.83)
24[d]	212-4	Chloroform	74	$C_{13}H_9N_3O_2$	65.26 (65.50)	3.79 (3.86)	17.56 (17.54)
25[d]	236-8	Acetic acid	82	$C_{14}H_{11}N_3O_3$	62.45 (62.30)	4.12 (4.15)	15.61 (15.43)
26[d]	249	Ethanol	84	$C_{13}H_9N_3O_2$	65.27 (65.27)	3.79 (3.96)	17.57 (17.34)
27[d]	320-2	DMF[b]	80	$C_{13}H_8N_4O_4$	54.93 (54.76)	2.84 (2.93)	19.71 (19.73)

[a]see **Scheme-I**; [b]dimethyl formamide; [c]reaction time 6 h; [d]reaction time 10 h.

TABLE-2
SPECTROSCOPIC DATA OF PRODUCTS[a]

Compd. No.	IR (ν_{max}, cm^{-1})[b]	^1H NMR δ in ppm (*J* in Hz) (solvent)
10	3000-2500 (br., OH), 1700 and 1675 (C=O), 1645, 1580, 1520, 1490, 1480, 1450, 1265, 1200, 1180, 755, 730.	7.60 (m, 5H, Ar), 8.50 (s, 1H, CH=C), 8.92 (s, 1H, H-3), 9.07 (s, 1H, H-5), (CF_3COOH)
11	3200-2500 (br., OH), 1710 and 1675 (C=O), 1640, 1580, 1520, 1380, 1260, 1180, 1015, 825, 725.	4.00 (t, 3H, OCH_3), 7.20 (d, 2H, *J* = 9.00, H-3' and H-5'), 7.60 (d 2H, J-9.00, H-2' and H-6'), 8.59 (s, 1H, CH=C), 9.00 (s, 1H, H-3), 9.03 (s, 1H, H-5), (CF_3COOH)
12	3400-2500 (br., NH and OH), 1725 and 1670 (C=O), 1585, 1470, 1445, 1270, 1200, 810, 765, 740, 695.	7.50 (m, 6H, NH and Ar), 7.95 (s, 1H, H-5), 8.22 (s, 1H, CH=C), (DMSO-d_6)
13[c]	3200-2500 (br., OH), 1730 (C=O), 1595, 1530 (NO_2), 1500, 1400, 1340 (NO_2), 1250, 1225, 1110, 950, 855, 815, 765, 750, 680, 670, 655.	–
14	1725 and 1710 (C=O), 1630, 1600, 1545, 1500, 1425, 1400, 1385, 1345, 1285, 1230, 1200, 1070, 1040, 1030, 1010, 955, 940, 870, 840, 760, 710, 690, 670.	1.30 (t, 3H, *J* = 7.00, -OCH_2CH_3), 1.35 (t, 3H, *J* = 7.00, -OCH_2CH_3), 4.28 (q, 2H, *J* = 7.00, -OCH_2CH_3), 4.38 (q, 2H, *J* = 7.00, -OCH_2CH_3), 7.55 (m, 6H, Ar and H-3), 7.86 (s, 1H, H-5), 8.23 (s, 1H, CH=C), ($CDCl_3$)
15	1710 (C=O), 1630, 1540, 1510, 1450, 1380, 1340, 1300, 1255, 1215, 1200, 1060, 1035, 1020, 1005, 955, 860, 840, 795, 750, 695, 655.	1.30 (t, 3H, *J* = 7.00, -OCH_2CH_3), 1.35 (t, 3H, *J* = 7.00, -OCH_2CH_3), 3.83 (s, 3H, OCH_3), 4.28 (q, 2H, *J* = 7.00, -OCH_2CH_3), 4.38 (q, 2H, *J* = 7.00, -OCH_2CH_3), 6.95 (d, 2H, *J* = 9.00, H-3' and H-5'), 7.58 (d, 2H, *J* = 9.00, H-2' and H-6'), 7.65 (s, 1H, H-3), 7.83 (s, 1H, H-5), 8.13 (s, 1H, CH=C), ($CDCl_3$)
16	1730 and 1700 (C=O), 1630, 1590, 1545, 1515 (NO_2), 1500, 1435, 1365, 1335 (NO_2), 1270, 1230, 1205, 1010, 950, 855, 750, 685, 660.	1.32 (t, 3H, *J* = 7.00, -OCH_2CH_3), 1.35 (t, 3H, *J* = 7.00, -OCH_2CH_3), 4.30 (q, 2H, *J* = 7.00, -OCH_2CH_3), 4.40 (q, 2H, *J* = 7.00, -OCH_2CH_3), 7.55-8.10 (m, 3H, H-2', H-6' and H-3), 8.15-8.55 (m, 3H, H-3', H-5' and H-5), 8.65 (s, 1H, CH=C), (CF_3COOH)
17	2210 (C≡N), 1610, 1600, 1535, 1500, 1450, 1420, 1255, 1245, 1190, 1025, 955, 905, 860, 750, 685, 660.	7.15-7.75 (m, 11H, arom. and H-3), 8.05 (s, 1H, H-5), 8.58 (s, 1H, CH=C), ($CDCl_3$)
18	2210 (C≡N), 1610, 1545, 1510, 1300, 1245, 1165, 1020, 960, 825, 755, 685, 655.	3.84 (s, 3H, OCH_3), 7.00 (d, 2H, *J* = 9.00, H-3' and H-5'), 7.20-7.80 (m, 8H, Ar and H-2' and H-6' and H-3), 8.28 (s, 1H, H-5), 8.56 (s, 1H, CH=C), ($CDCl_3$-CF_3COOH)
19	2210 (C≡N), 1610, 1595, 1520, 1500 (NO_2), 1440, 1405, 1385, 1335 (NO_2), 1255, 1190, 1110, 1020, 950, 860, 770, 750, 690.	7.20-7.80 (m, 9H, arom.), 8.38 (s, 1H, H-3), 8.45 (s, 1H, H-5), 8.85 (s, 1H, CH=C), (CF_3COOH)
20	2220 (C≡N), 1710 (C=O), 1610, 1590, 1535, 1505, 1430, 1400, 1385, 1275, 1205, 1010, 950, 870, 760, 725, 665.	1.40 (t, 3H, *J* = 7.00, -OCH_2CH_3), 4.35 (q, 2H, *J* = 7.00, -OCH_2CH_3), 7.20-7.80 (m, 6H, Ar and H-3), 8.23 (s, 1H, H-5), 8.75 (s, 1H, CH=C), ($CDCl_3$)
21	2220 (C≡N), 1710 (C=O), 1610, 1520, 1380, 1255, 1205, 1180, 1040, 1010, 870, 830.	1.40 (t, 3H, *J* = 7.00, -OCH_2CH_3), 3.88 (s, 3H, OCH_3), 4.35 (q, 2H, *J* = 7.00, -OCH_2CH_3), 6.98 (d, 2H, *J* = 9.00, H-3' and H-5'), 7.63 (d, 2H, *J* = 9.00, H-2' and H-6'), 8.20 (s, 2H, H-3 and H-5), 8.65 (s, 1H, CH=C), ($CDCl_3$)
22	3250 (NH), 2220 (C≡N), 1710 (C=O), 1600, 1530, 1480, 1430, 1260, 1010, 890, 770, 760, 730, 700, 670.	1.35 (t, 3H, *J* = 7.00, -OCH_2CH_3), 4.30 (q, 2H, *J* = 7.00, -OCH_2CH_3), 7.50 (s, 5H, Ar), 8.17 (s, 1H, H-5), 8.65 (s, 1H, CH=C) ($CDCl_3$)
23	2210 (C≡N), 1725 (C=O), 1590, 1510 (NO_2), 1395, 1370, 1335 (NO_2), 1305, 1240, 1175, 1105, 1025, 950, 855, 750.	1.30 (t, 3H, *J* = 7.00, -OCH_2CH_3), 4.15 (q, 2H, *J* = 7.00, -OCH_2CH_3), 7.75 (s, 1H, H-3), 7.80 (d, 2H, *J* = 9.00, H-2' and H-6'), 7.95 (s, 1H, H-5), 8.25 (s, 1H, CH=C), 8.35 (d, 2H, *J* = 9.00, H-3' and H-5') ($CDCl_3$)
24	3300-2500 (br., OH), 2220 (C≡N), 1710 (C=O), 1605, 1590, 1540, 1495, 1375, 1325, 1270, 1220, 1180, 1020, 755, 705.	7.58 (m, 5H, Ar), 8.35 (s, 1H, H-3), 8.43 (s, 1H, H-5), 8.78 (s, 1H, CH=C), ($CDCl_3$-CF_3COOH)
25	3200-2800 (br., OH), 2220 (C≡N), 1685 (C=O), 1600, 1535, 1510, 1380, 1290, 1220, 1175, 755, 715.	3.95 (s, 3H, OCH_3), 7.12 (d, 2H, *J* = 9.00, H-2 and H-6), 7.60 (d, 2H, *J* = 9.00, H-3 and H-5), 8.48 (s, 1H, H-3), 8.56 (s, 1H, H-5), 8.75 (s, 1H, CH=C), (CF_3COOH)
26	3290 (br., NH), 3000-2400 (br., OH), 2220 (C≡N), 1695 (C=O), 1600, 1480, 1280, 1265, 1235, 1010, 950, 880, 775, 710, 695, 970.	7.71 (m, 6H, Ar and NH), 8.49 (s, 1H, H-5), 9.25 (s, 1H, CH=C), (CF_3COOH)
27[c]	3200 (br., OH), 2230 (C≡N), 1710 (C=O), 1610, 1590, 1550, 1520 (NO_2), 1495, 1335 (NO_2), 1235, 1080, 850, 750, 695.	–

[a]See **Scheme-1**; [b]all strong bands; [c]not very soluble in common NMR solvents.

during the reactions. As can be seen from the yields of the products (Table-1), the condensations worked well with the carbaldehydes studied. The following "active methylene" compounds were used: malonic acid, diethyl malonate, phenylacetonitrile, ethyl cyanoacetate and cyanoacetic acid. For the compounds (**21-23**) obtained during these reactions the yields were low but can be improved by increasing the reaction time as was the case with compounds (**17-19** and **24-27**).

The Knoevenagel reaction when carried out between an aldehyde and malonic acid or cyanoacetic acid in the presence of pyridine-piperidine catalyst at water bath temperature usually leads to the corresponding acrylic acid or acrylonitrile,

respectively by undergoing decarboxylation during the reaction. The non-decarboxylated products in the earlier reported reactions have been isolated by conducting the reactions at room temperature and with ammonia as catalyst[1]. However, in our present work, we found that the reactions carried out with these pyrazole-4-carbaldehydes with pyridine-piperidine catalyst in refluxing ethanol also gave the non-decarboxylated products (**10-13** and **24-27**) in good yields. No decarboxylated products were isolated from these reactions. All isolated products were well characterized through their Infrared absorption (IR) and proton magnetic resonance spectra (NMR) were consistent with the structures (Table-2).

It may be noted that some recent publications deal with the Knoevenagal reaction of pyrazole-4-carbaldehydes with malonic acid under microwave irradiation giving the corresponding acrylic acids[26].

IR spectra: With the help of IR spectra (Table-2) it was easy to confirm the presence of carboxylic group in products. There were two carbonyl peaks appearing in between 1730-1675 cm^{-1} in case of dicarboxylated compounds and a broad peak at 3000-2500 cm^{-1} for -OH group. This points out that no decarboxylation has taken place during the condensation and pointing to the structures as (**10-13** and **24-27**). For -NO_2 group containing compounds two bands appeared in the region of 1545-1495 cm^{-1} (asymmetric stretching) and 1350-1310 cm^{-1} (symmetric stretching).

^{1}H NMR spectra: The PMR spectra were very helpful in elucidating structures of the products of condensation and readily confirmed the absence of decarboxylation during the reaction. The PMR spectra showed a singlet between 8.10 and 9.25 due to a single vinyl proton instead of two doublets expected for the two vinyl protons in case a decarboxylation would have occurred. All the products (**10-13** and **24-27**) displayed this feature. Other signals due to the remaining groups, aryl and pyrazole protons were also easily identified[27] (Table-2).

Conclusion

Knoevenagel condensation of pyrazole-4-carbaldehydes and various "active methylene" compounds using pyridine and piperidine as base in refluxing ethanol were studied during this research work (**Scheme-I**). In the present study condensations with malonic acid or cyanoacetic acid did not accompany decarboxylations and the expected products retaining the carboxylic groups were isolated. IR, ^{1}H NMR and elemental analysis helped in characterizing these products. In some cases yields are improved by increasing reaction times.

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