A NEW AND FACILE SYNTHESIS OF 5-ARYLPYRIMIDINES AND 4-ARYLPYRAZOLES

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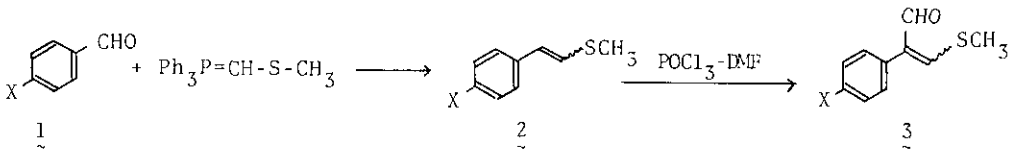
Abstract —— A condensation of 2-aryl-3-(methylthio)acroleins (3a)-(3e), a new masked form of arylmalondialdehydes, with amidines yielded the corresponding 5-arylpyrimidines (4a)-(4k). Similarly, the reaction of 3 with N-substituted hydrazines gave the corresponding 1-substituted 4-arylpyrzolones (5a)-(5j).

Considerable efforts have been directed toward the synthesis of a number of pyrimidine derivatives owing to their attractive biological importance and many detailed reviews have appeared[1,2]. Of synthetic strategies, the condensation of 1,3-dicarbonyl compounds or their masked form with N-C-N fragments are known as the most widely applicable method offering direct entry into pyrimidine nucleus. Recently, a series of 5-aryl and 4-substituted 5-arylpyrimidine derivatives[3,4,5] were appeared aimed at a synthesis of antiinflammatory active compounds by Sandoz group. We investigated a synthesis of a new masked form of arylmalondialdehydes, easily available from arylaldehydes[6] and its application to a synthesis of 5-arylpyrimidines for the biological evaluations. The method was also applied to a synthesis of 4-arylpyrazoles by the reaction with N-substituted hydrazines instead of amidines. We wish to report the results of our studies in this paper.

First, we prepared 2-aryl-3-(methylthio)acroleins (3a)-(3e), common synthetic intermediates for the synthesis of 5-arylpyrimidines and 4-arylpyrazoles as outlined in the Scheme 1. The Wittig reaction[7] of arylaldehydes (1a)-(1e) with triphenylphosphonium thiomethylmethylide[8], derived from methylthiomethyltriphenylphosphonium chloride [n-BuLi, THF, 0°C-room temperature, 1 hr, then aldehydes at 0°C, room temperature, 14 hr] afforded the corresponding 2-arylethenyl methyl sulfides (2a)-(2e), respectively. The Vilsmeier reaction of 2 by the $POCl_3$-DMF procedure

afforded the corresponding 2-aryl-3-(methylthio)acroleins (3a)-(3e)[9], respectively. The yields and physical data of 2 and 3 are listed in the Table 1.



1 2 3

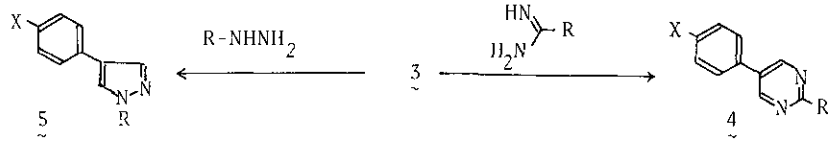
Scheme 1

Table 1. Yields and physical data of 2 and 3.

	1	2		3		
	X	Yield (%)	mp (°C) or bp (°C/torr)	Yield (%)	mp (°C) or bp (°C/torr)	NMR ($CDCl_3$) Spectra[a] δ
a	CH_3	92	35-37[b]	91	70-71	2.35 (3H, s), 2.45 (3H, s), 9.38 (1H, s)
b	OCH_3	90	70[c]	92	189-195/3	2.30 (3H, s), 3.68 (3H, s), 9.36 (1H, s)
c	F	90	106-11/3	93	85-86	2.38 (3H, s), 9.38 (1H, s)
d	Cl	92	47[d]	95	88-89	2.40 (3H, s), 9.35 (1H, s)
e	CO_2Et	92	158-160/3	86	47-48	2.32 (3H, s), 9.37 (1H, s)

a Only characteristic signals are given. b Ref.[10] mp 35-37°C. c Ref.[10] mp 72-73°C. d Ref.[11] mp 47°C.

Condensation of 3 with formamidine acetate (2 eq.) in EtOH in the presence of Na_2CO_3 (2 eq. mol) under reflux for 6 hr yielded the corresponding 5-arylpyrimidines (4a)-(4e). The same reaction by the use of acetamidine hydrochloride instead of formamidine acetate afforded the corresponding 5-aryl-2-methylpyrimidines (4f)-(4j). The reaction of 3d with guanidine hydrochloride under the same conditions as above gave 4k. The yields and physical data of these pyrimidines are listed in the Table 2. Compounds (3a)-(3e) were also applied to a synthesis of 4-arylpyrazoles. Treatment of 3 with N-monosubstituted hydrazine (2 eq.) in EtOH under reflux for 14 hr yielded the corresponding 1-substituted 4-arylpyrazoles (5a)-(5j) (Scheme 2). Yields and physical data are listed in the Table 3.



5 3 4

Scheme 2

From these results, 2-aryl-3-(methylthio)acroleins are found to be useful masked form of arylmalondialdehydes as existing analogues such as 2-aryl-3-(dimethylamino)acroleins[5]. Antiinflammatory activity of 4 will be reported elsewhere.

Table 2. Yields and physical data of 4a-4k

	4 X	R	Yield (%)	mp (°C)	NMR ($CDCl_3$) Spectra[a] δ
a	CH_3	H	92.3	74-75	2.43 (3H, s), 8.92 (2H, s), 9.17 (1H, s)
b	OCH_3	H	94.2	111-111.5	3.86 (3H, s), 8.95 (2H, s), 9.18 (1H, s)
c	F	H	91.8	99-100	8.92 (2H, s), 9.18 (1H, s)
d	Cl	H	94.3	154-155	8.93 (2H, s), 9.20 (1H, s)
e	CO_2Et	H	85.6	61-62	8.92 (2H, s), 9.22 (1H, s)
f	CH_3	CH_3	95.0	108-109	2.42 (3H, s), 2.77 (3H, s), 8.87 (2H, s)
g	OCH_3	CH_3	93.5	138-139	2.76 (3H, s), 3.84 (3H, s), 8.83 (2H, s)
h	F	CH_3	93.3	154-155	2.80 (3H, s), 8.91 (2H, s)
i	Cl	CH_3	90.9	172-173	2.80 (3H, s), 8.83 (2H, s)
j	CO_2Et	CH_3	88.3	118-119	2.85 (3H, s), 8.95 (2H, s)
k	F	NH_2	75.9	185-186[b]	

a Only characteristic signals are given. b Ref.[12] mp 185-187°C.

Table 3. Yields and Physical data of 5

	5 X	R	Yield (%)	mp (°C)	NMR ($CDCl_3$) Spectra δ N-CH_3	3-H	5-H
a	CH_3	CH_3	90	106-107	3.92	7.66	7.50
b	OCH_3	CH_3	92	139-140	3.80	7.63	7.47
c	F	CH_3	93	101-102	3.93	7.67	7.52
d	Cl	CH_3	96	97-98	3.93	7.65	7.50
e	CO_2Et	CH_3	90	108-109	3.95	7.77	7.63
f	CH_3	C_6H_5	50	127-128		8.03	7.90
g	OCH_3	C_6H_5	60	172-173		8.00	7.90
h	F	C_6H_5	88	109-110		8.08	7.92
i	Cl	C_6H_5	95	126-127		8.10	7.93
j	CO_2Et	C_6H_5	92	127-128		8.08	7.97

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