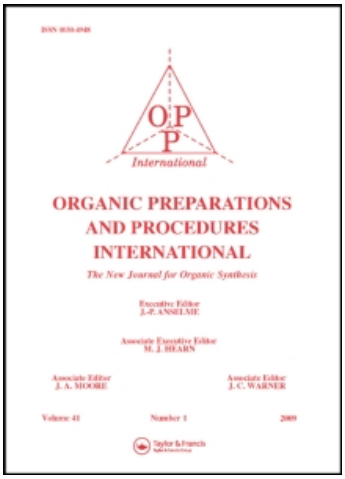

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ENAMINONES IN THE SYNTHESIS OF HETEROCYCLES BY MICROWAVE IRRADIATION

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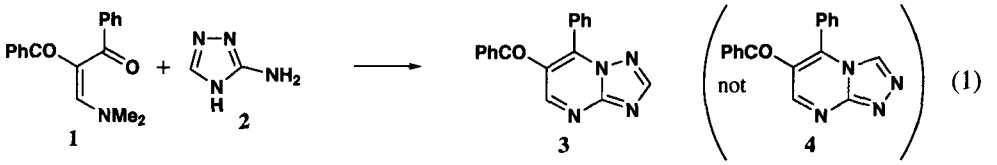
The utility of enaminones for the synthesis of aromatic heterocycles has received considerable interest over the past few years.[1-5] Enaminones have been shown to be excellent precursors of pyranones[6] 2-oxopyridine carbonitriles,[7] isoxazoles,[8] pyrimidines[9] and azolopyrimidines.[10-12] In conjunction with the utility of enaminones in building aromatic heterocycles as potential agrochemicals,[13,14] we now report on the use of 2-dimethylaminomethylene-1,3-diphenylpropane-1,3-dione (**1**)[15] for synthesis of azolopyrimidines, and pyranones under microwave heating "green technology"[16,17] in the absence of solvent and compare the yields and the structure of the products with those obtained *via* conventional heating.

Thus **1** reacted with 3-amino-1,2,4-triazole (**2**) both by reaction under radiation in a domestic microwave oven for 2 minutes or by reflux for 1 hour in ethanol to yield one product that may be formulated as **3** or its isomeric structure **4** (*Eq. 1*). Although in similar work with

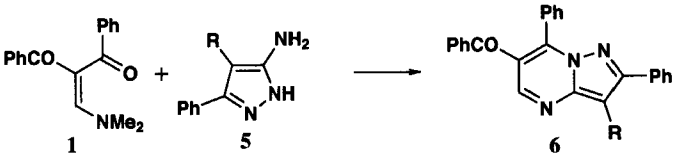


(1)

enaminones[18,19] structure **4** was assumed to be the product. In our hands, 1,2,4-triazolo[1,5-a] pyrimidine structure (**3**) was shown to be the product based on an X-ray crystal structure, especially after ^{1}H NMR indicated triazole and pyrimidine CH at δ 8.9 and δ 8.6 which are very similar to the values reported for the isomeric **4**.

The reaction of **1** with 1H-5-aminopyrazole (**5**) afforded the pyrazolo[1,5-a] pyrimidine derivative **6** (*Eq. 2*).

Similar to its behavior toward aminopyrazole and aminotriazole, compound **1** reacted with aminobenzimidazole **7** to yield the benzimidazolopyrimidine derivative **8** and not **9**.[20] ^{1}H NMR confirmed structure **8** as it revealed two high field doublets at δ 6.2 and 6.5 for H-Ph and



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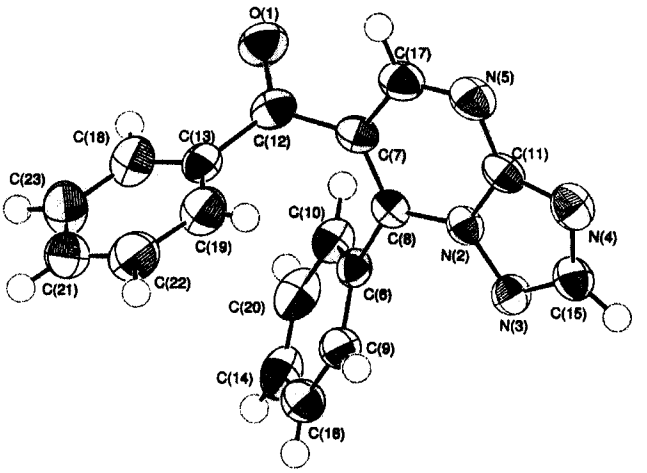
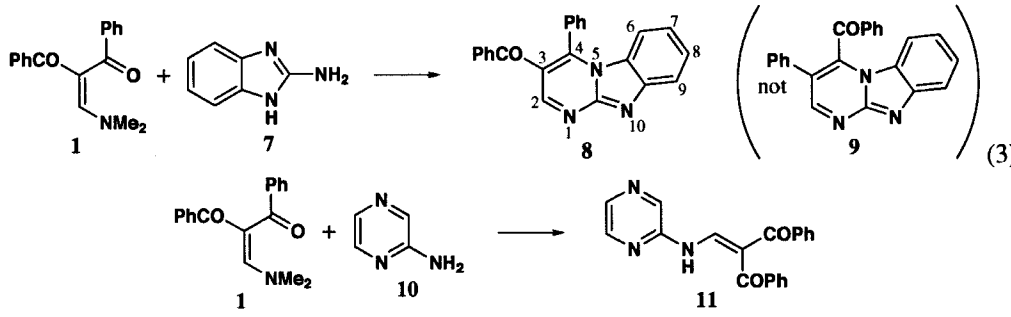


X-ray Crystal Structure of Compound 3

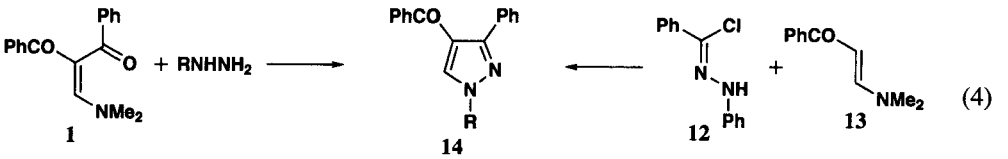
Fig. 1

benzimidazolyl H-6 and at δ 8.9 for H-2. If the product was the isomer structure **9**, it would be difficult to account for the appearance of these signals at such high fields.[20] Shielding of these two protons is a result of ring current anisotropy of phenyl ring at C-4, and the chemical shift of H-2 of the pyrimidine ring at δ 9.55. Only enaminone **11** was obtained from reaction of **10** with **1** (*Eq. 3*).



(3)

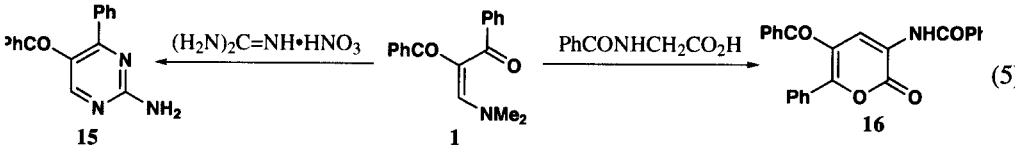
The reaction of **1** with phenylhydrazine afforded a product formulated as **14**.[15,16] Structure **14** was preferred over possible isomeric form based on its identity with the product of the reaction of hydrazonylchloride **12** with the enaminones **13**, whose regiochemistry has been established previously.[13]



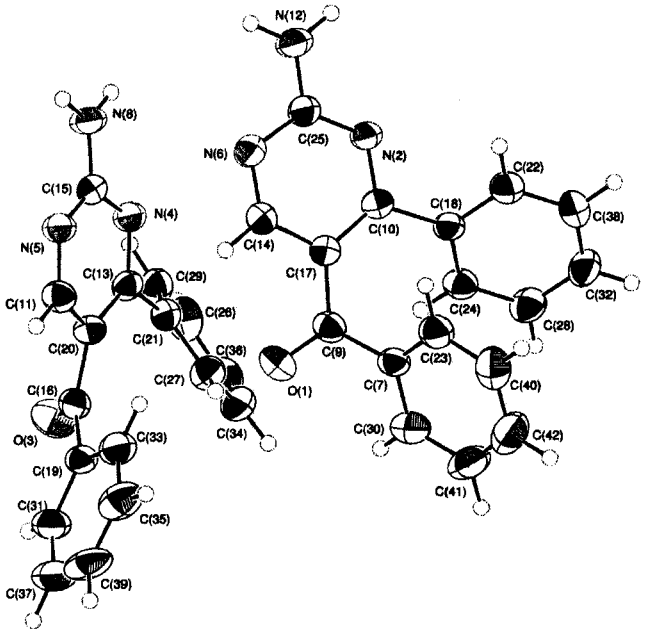
(4)

a) R = H; b) R = Ph

Compound **1** reacted with guanidine nitrate to yield pyrimidine[9] **15**, the structure of which was established by X-ray crystal structure, while reaction with hippuric acid in refluxing acetic acid anhydride yielded pyranone derivative **16** (*Eq. 5*) whose structure was confirmed by elemental analyses and spectral data (*Tables 1,2*).



(5)



X-ray Crystal Structure of Compound 15

Fig. 2

Acknowledgement.- The author is grateful to Prof. M. H. Elnagdi for his support, comments and continued help.

EXPERIMENTAL SECTION

All melting points were measured on Gallenkamp electrothermal melting point apparatus and are uncorrected. Microwave synthesis were carried out in Microwave oven SJO390W. IR spectra

were obtained as KBr pellets on a Pye Unicam SP 3-300 Spectrophotometer. ^{1}H NMR spectra were recorded in *DMSO*-d_6 or $CDCl_3$ at 200 and 300 MHz on Varian Gemini NMR spectrometers using tetramethylsilane (*TMS*) as an internal reference and results are expressed as δ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. DMFDMA is a commercial material purchased from Ubichem.

2-Dimethylaminomethylene-1,3-diphenylpropane-1,3-dione (1). Method A.- A mixture of 1,3-diphenylpropane-1,3-dione (2.24 g, 10 mmol) with dimethylformamide dimethylacetal (DMFDMA) (1.19 g, 10 mmol) in dry toluene (50 mL) was heated under reflux for 8 h, then left to cool to room temperature. The solid orange product so formed was collected by filtration, and recrystallized from dioxane.

Method B.- A mixture of 1,3-diphenylpropane-1,3-dione (2.24 g, 10 mmol) with DMFDMA (1.19 g, 10 mmol) was irradiated in a domestic microwave oven for 4 minutes. The resulting product was washed with ethanol and recrystallized from dioxane. Compound **1** was obtained as orange crystals (85%), mp 120-122°C, *lit.*[15] mp 120°C (45% Yield).

General Procedure for the Preparation of Compounds 3,6,8,11. Method A.- A mixture of each 2-dimethylaminomethylene-1,3-diphenylpropane-1,3-dione (2.7 g, 10 mmol) and the heterocyclic amine (**2, 5a,b, 7** or **10**) (10 mmol) was heated at 120°C for 1 h. The reaction mixture was left to cool and the solid was triturated with ethanol. The solid product was collected and recrystallized from ethanol/dioxane.

Method B.- A mixture of 2-dimethylaminomethylene-1,3-diphenylpropane-1,3-dione (2.7 g, 10 mmol) and the heterocyclic amine (**2, 5a,b, 7** or **10**) (10 mmol) was placed in the microwave oven and irradiated for 2-3 min, then the reaction mixture was triturated with ethanol and the solid products formed were collected and recrystallized from ethanol/dioxane to afford the following products, respectively.

Phenyl-(7-phenyl[1,2,4]triazolo[1,5-a] pyrimidin-6-yl)methanone (**3**), (2,7-diphenyl-1,3-dihydropyrazolo[1,5-a]pyrimidin-6-yl)phenylmethanone (**6a**), (3-bromo-2,7-diphenylpyrazolo[1,5-a]pyrimidin-6-yl)phenylmethanone (**6b**), phenyl-(4-phenyl-benzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)methanone (**8**) and 1,3-diphenyl-2-(pyrazin-2-ylaminomethylene)propane-1,3-dione (**11**).

Phenyl-(3-phenyl-1H-pyrazol-4-yl)methanone (14a), Phenyl-(1,3-diphenyl-1H-pyrazol-4-yl)methanone (14b). Method A.- A mixture of 2-dimethylaminomethylene-1,3-diphenylpropane-1,3-dione (2.7 g, 10 mmol) was treated with hydrazine hydrochloride (1.04 g, 10 mmol) or phenylhydrazine (1.08 g, 10 mmol) and refluxed in ethanol for 1 h. The solid product obtained was filtered off and recrystallized from ethanol.

Method B.- A mixture of 2-dimethylaminomethylene-1,3-diphenylpropane-1,3-dione (2.7 g, 10 mmol) with phenylhydrazine (1.08 g, 10 mmol) was irradiated in a domestic microwave oven for 3 minutes. The resulting product was washed with ethanol and recrystallized from ethanol. (mp mixed mp and TLC) mp 156-158°C, *lit.* [15] mp 153°C.

(2-Amino-4-phenylpyrimidin-5-yl)phenylmethanone (15). Method A.- To a solution of 2-

dimethylaminomethylene-1,3-diphenylpropane-1,3-dione (2.7 g, 10 mmol) in absolute ethanol (30 mL), guanidine nitrate (0.95 g, 10 mmol) and potassium carbonate anhydrous (0.53 g, 20 mmol) were added. The mixture was heated under reflux for 8 h. The solid product obtained was collected and recrystallized from ethanol, mp 169-171°C, *lit.*[9] mp 164°C.

Method B.- A mixture of 2-dimethylaminomethylene-1,3-diphenylpropane-1,3-dione (2.7 g, 10 mmol), guanidine nitrate (0.95 g, 10 mmol) and potassium carbonate anhydrous (0.53 g, 20 mmol) was placed in the microwave oven and irradiated for 5 min, then the reaction mixture was left to cool at room temperature. The formed solid products were collected and recrystallized from ethanol.

N-(5-Benzoyl-2-oxo-6-phenyl-5,6-dihydro-2H-pyran-3-yl)benzamide (16). Method A.- A mixture of 2-dimethylaminomethylene-1,3-diphenylpropane-1,3-dione (2.7 g, 10 mmol) and hippuric acid (1.79 g, 10 mmol) in dry acetic anhydride (30 mL) was refluxed for 3-4 h. The solid product obtained upon cooling was isolated by filtration and recrystallized from ethanol.

Method B.- A mixture of 2-dimethylaminomethylene-1,3-diphenylpropane-1,3-dione (2.7 g, 10 mmol) and hippuric acid (1.79 g, 10 mmol) was placed in the microwave oven and irradiated for 6 min, then the reaction mixture was left to cool at room temperature. The formed solid products were collected and recrystallized from ethanol.

Table 1. Physical Data for New Compounds

Cmpd	Yield (%)	mp (°C)	Elemental Analyses (Found) C	H	N
1	85	120-122[a]	77.40 (77.39)	6.13 (6.09)	5.01 (5.02)
3	90	204-206[b]	71.99 (72.0)	4.03 (4.01)	18.66 (18.65)
6a	90	200-203[b]	79.98 (79.97)	4.56 (4.59)	11.19 (11.12)
6b	80	269-270[b]	66.09 (66.07)	3.55 (3.51)	9.25 (9.21)
8	80	259-260[b]	79.07 (79.08)	4.33 (4.29)	12.03 (12.04)
11	80	259-262[b]	72.94 (72.93)	4.59 (4.55)	12.76 (12.77)
14a	80	156-158[c]	77.40 (77.41)	4.87 (4.83)	11.28 (11.29)
14b	80	156-158[c]	81.46 (81.48)	4.97 (4.91)	8.64 (8.66)
15	80	169-171[c]	74.17 (74.18)	4.76 (4.72)	15.26 (15.27)
16	80	146-149[c]	75.94 (75.94)	4.33 (4.30)	3.54 (3.59)

a) from dioxane, b) from dioxane-ethanol, c) from ethanol.

Table 2: Spectral Data for New Compounds

Cmpd	IR (cm^{-1})	^1HNMR (d_H)	m/e
1	1725 (CO)	2.47 (s, 6H, $2CH_3$), 7.4-7.8 (m, 10H, Ar-H), 7.88 (s,1H, = CHN)	279
3	1710 (CO)	7.30-7.67 (m, 10H, Ar-H), 8.60 (s, 1H, H-2), 8.98 (s, 1H, H-5)	300
6a	1700 (CO)	7.33-7.73(m, 16H, Ar-H, H-3), 8.65 (s, 1H, H-5)	376 ($M^+ + 1$)
6b	1700 (CO)	7.30-8.0 (m, 15H, Ar-H), 8.75 (s, 1H, H-5)	453 ($M^+ - 1$)
8	1695 (CO)	6.2 (d, 1H, H-Ph), 6.59 (d, 1H, H-6 benzimidazole), 7.4-7.8 (m, 12H, Ar-H), 8.9 (s, 1H, H-2)	349
11	1680 (CO), 3255 (NH)	7.24-7.75 (m, 10H, Ar-H), 8.28 (d, 1H, H-5), 8.32 (d, 1H, H-6), 8.39 (s, 1H, H-3), 8.78 (d, 1H, olefinic H), 12.1 (d, 1H, NH)	328 ($M^+ - 1$)
14a	1680 (CO), 3220 (NH)	7.35-7.76 (m, 10H, Ar-H), 8.07 (b, H, H-5), 13.51(s, 1H, NH)	248
14b	1690 (CO)	7.23-7.8 (m, 15H, Ar-H), 8.04 (s, 1H, H-5)	323 ($M^+ - 1$)
15	1700 (CO), 3500 (NH_2)	5.95 (s, 2H, NH_2), 7.24-7.64 (m, 10H, Ar-H), 8.53 (s, 1H, H-6)	274 ($M^+ - 1$)
16	3306 (NH), 1719 (ring CO), 1680 (CO), 1676 (amide CO)	7.95 (s, 1H, NH), 7.33-8.18 (m, 15H, Ar-H), 9.80 (s, 1H, H-4)	396 ($M^+ + 1$)

Table 3. Comparison of Reaction Times and Yields by Conventional and Microwave Heating

	Conventional Δ		Microwave Δ	
Cmpd	Yield (%)	Time (min.)	Yield (%)	Time (min.)
1	70	480	85	4
3	80	60	90	2
6a	70	60	90	3
6b	65	60	80	2
8	70	60	80	2
11	60	60	80	2
14b	70	60	80	3
15	70	480	80	5
16	75	240	80	6

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