A Simple Regioselective Synthesis of Pyrimido[1,2-a]benzimidazoles

Shin-Shyong Tseng*, Joseph W. Epstein,

Herbert J. Brabander and Gerardo Francisco

Cardiovascular-CNS Disease Research Section, American Cyanamid Company,
Medical Research Division, Lederle Laboratories
Pearl River, N.Y. 10965
Received October 6, 1986

2-Aminobenzimidazoles were reacted with enaminones in acetic acid to give pyrimido[1,2-a]benzimidazoles. With a substituted enaminone only one regioisomer was obtained. Structural assignments based on nmr and uv spectroscopy are presented. Possible pathways leading to the products are discussed.

Syntheses of the ring systems containing a pyrimido-[1,2-a]benzimidazole are largely based on ring closure reactions of 2-aminobenzimidazole derivatives with ß-diketones [1]. The use of unsymmetrical ß-dicarbonyl compounds in such annulation reactions can lead to two possible pyrimido[1,2-a]benzimidazole products [1-4].
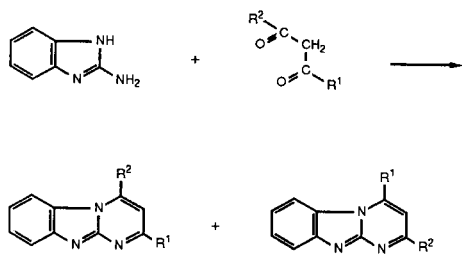
Now we wish to report a regioselective synthesis of pyrimido[1,2-a]benzimidazole by the reaction of 2-aminobenzimidazole with a variety of enaminones in refluxing acetic acid.

Results and Discussion.

The enaminones were prepared in good to excellent yields by the one-step reaction of ring-substituted acetophenones with N,N-dimethylformamide dimethyl acetal or N,N-dimethylacetamide dimethyl acetal. When N,N-dimethylbenzamide diethyl acetal was used, the corresponding enaminones were obtained in moderate yields (Table I). N,N-dimethylbenzamide diethyl acetal was prepared according to the procedure of Parker *et al* [5]. The structures of the enaminones were confirmed by spectroscopic data and elemental analyses.
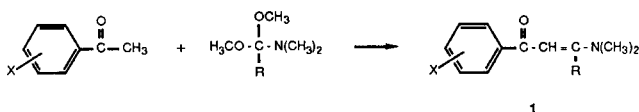

The formation of enaminones by the reaction of aryl methyl ketones and formamide acetal has been known for some time; these are versatile synthons for the synthesis of

a number of novel heterocycles [6-10]. Bredereck and his coworkers reported that the enaminone, derived from acetophenone upon treatment with guanidine carbonate in the presence of sodium ethoxide and ethanol, afforded 2-amino-4-phenylpyrimidine in good yield [6]. 2-Aminobenzimidazole, which contains a guanidine moiety, may
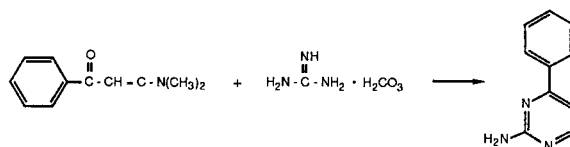
be expected to react with an enaminone in a similar manner. In fact, we found that when 2-aminobenzimidazole was refluxed with an enaminone **1** in glacial acetic acid, the expected ring closure reaction was observed, and the regiochemistry of the products was controlled by the nature of the R group in enaminone **1**. When R is a hydrogen, the two possible isomeric pyrimido[1,2-a]benzimidazoles **2** and **3** were obtained in about equal amounts. The products **2** and **3** were isolated by preparative hplc or by
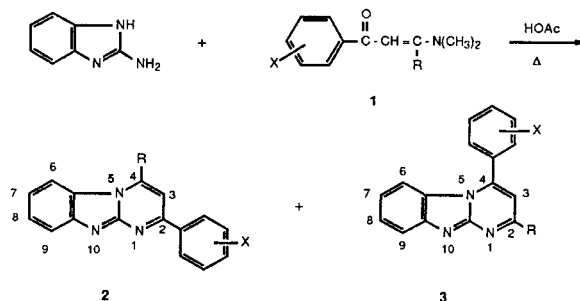

flash column chromatography, and were further purified by recrystallization. The total isolated yields of **2** and **3** were in the range of 40 to 50% (Table II). The regioselectivity of the ring closure reaction was clearly observed when R is either a methyl or a phenyl group; only isomer **3** was formed and isolated. When R is a methyl group and X is a m-CF$_3$, a m-Cl or a p-CH$_3$ group, trace amounts (1-2%) of the isomers **2** (*i.e.*, **2g**, **2h** or **2i**) were also isolated.

Table I

Enaminones **1**
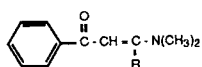
Compound Number	X	R	Yield, %	mp °C	bp °C/mm Hg	Formula [a]
1a	m-CF$_3$	H	82	58-60		$C_{12}H_{12}F_3NO$
1b	m-Cl	H	84	68-70		$C_{11}H_{12}ClNO$
1c	p-Cl	H	84	81-83		$C_{11}H_{12}ClNO$
1d	p-CH$_3$	H	63	93-95		$C_{12}H_{15}NO$
1e	m-OCH$_3$	H	86		118-120/0.025	$C_{12}H_{15}NO_2$
1f	H	H	58	88-90		$C_{11}H_{13}NO$
1g	m-CF$_3$	CH$_3$	88	56-58		$C_{13}H_{14}F_3NO$
1h	m-Cl	CH$_3$	70	49-51		$C_{12}H_{14}ClNO$
1i	p-Cl	CH$_3$	88	103-105		$C_{12}H_{14}ClNO$
1j	p-CH$_3$	CH$_3$	57	100-102		$C_{13}H_{17}NO$
1k	H	CH$_3$	55	61-63		$C_{12}H_{15}NO$
1ℓ	m-CF$_3$	C$_6$H$_5$	40		130-153/0.1	$C_{18}H_{16}F_3NO$
1m	m-Cl	C$_6$H$_5$	42		170-175/0.5	$C_{17}H_{16}ClNO$
1n	p-Cl	C$_6$H$_5$	40		180-185/0.05	$C_{17}H_{16}ClNO$
1o	p-CH$_3$	C$_6$H$_5$	43		165-170/0.45	$C_{18}H_{19}NO$
1p	p-OCH$_3$	C$_6$H$_5$	35		120-125/0.3	$C_{18}H_{19}NO_2$
1q	H	C$_6$H$_5$	44		160-165/0.06	$C_{17}H_{17}NO$

[a] See Table V for the analytical data.

Table II

Pyrimido[1,2-a]benzimidazoles **2** and **3**
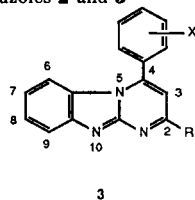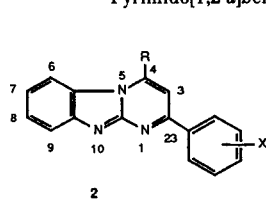
Compound Nummber	X	R	Yield, % isolated	mp °C	Formula [a]
2a	m-CF$_3$	H	20	271-273	$C_{17}H_{10}F_3N_3$
3a	m-CF$_3$	H	21	197-199	$C_{17}H_{10}F_3N_3$
2b	m-Cl	H	27	275-277	$C_{16}H_{10}ClN_3$
3b	m-Cl	H	29	196-198	$C_{16}H_{10}ClN_3$
2c	p-Cl	H	23	316-318	$C_{16}H_{10}ClN_3$
3c	p-Cl	H	26	178-180	$C_{16}H_{10}ClN_3$
2d	p-CH$_3$	H	23	306-308	$C_{17}H_{13}N_3$
3d	p-CH$_3$	H	29	167-169	$C_{17}H_{13}N_3$
2e	m-OCH$_3$	H	23	201-203	$C_{16}H_{13}N_3O$
3e	m-OCH$_3$	H	26	193-195	$C_{16}H_{13}N_3O$
2f	H	H	20	287-289	$C_{16}H_{11}N_3$
3f	H	H	23	163-165	$C_{16}H_{11}N_3$
2g	m-CF$_3$	CH$_3$	1.1	251-253	$C_{18}H_{12}F_3N_3$

Table II (continued)

Compound Number	X	R	Yield, % isolated	mp °C	Formula [a]
3g	m-CF$_3$	CH$_3$	53	231-233	$C_{18}H_{12}F_3N_3$
2h	m-Cl	CH$_3$	1.5	252-254	$C_{17}H_{12}ClN_3$
3h	m-Cl	CH$_3$	49	216-218	$C_{17}H_{12}ClN_3$
3i	p-Cl	CH$_3$	38	218-220	$C_{17}H_{12}ClN_3$
2j	p-CH$_3$	CH$_3$	1.8	251-253	$C_{18}H_{15}N_3$
3j	p-CH$_3$	CH$_3$	48	171-173	$C_{18}H_{15}N_3$
3k	H	CH$_3$	44	203-205	$C_{17}H_{13}N_3$
3ℓ	m-CF$_3$	C$_6$H$_5$	50	237-239	$C_{23}H_{14}F_3N_3$
3m	m-Cl	C$_6$H$_5$	56	242-244	$C_{22}H_{14}ClN_3$
3n	p-Cl	C$_6$H$_5$	72	221-223	$C_{22}H_{14}ClN_3$
3o	p-CH$_3$	C$_6$H$_5$	40	220-222	$C_{23}H_{17}N_3$
3p	p-OCH$_3$	C$_6$H$_5$	58	218-220	$C_{23}H_{17}N_3O$
3g	H	C$_6$H$_5$	61	311-313 [b]	$C_{22}H_{15}N_3$

[a] See Table V for the analytical data.   [b] Literature mp 312-315° [1].

Table III

^{1}H NMR Spectral Data of some Pyrimido[1,2-a]benzimidazoles [a]
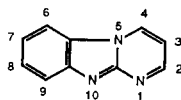
Compound Number	2	3	4	6	7	8	9
2a	m-CF$_3$-C$_6$H$_4$ 7.69 (t), 1H, J = 7.6; 7.79 (d), 1H, J = 8.0 8.00 (d), 1H, J = 8.0; 8.50 (s), 1H	7.44 (d) J = 7.2	8.82 (d) J = 7.2	8.47 (d) J = 8.1	7.44 (t) J = 7.6	7.60 (t) J = 7.6	7.90 (d) J = 8.1
3a	8.83 (d) J = 4.1	6.78 (d) J = 4.1	m-CF$_3$-C$_6$H$_4$ 7.63-8.07 (m) 4H	6.73 (d) J = 8.1	7.09 (t) J = 7.6	7.50 (t) J = 7.6	7.90 (d) J = 8.1
2f	C$_6$H$_5$ 7.35-7.55 (m), 3H; 7.80 (d), 1H, J = 8.0 8.25 (d), 1H, J = 8.0	7.45 (d) J = 7.2	8.70 (d) J = 7.2	8.25 (d) J = 8.1	7.45 (t) J = 7.6	7.50 (t) J = 7.6	7.95 (d) J = 8.1
3f	8.70 (d) J = 4.1	6.70 (d) J = 4.1	C$_6$H$_5$ 7.57 (bs) 5H	6.62 (d) J = 8.1	6.96 (t) J = 7.6	7.30 (t) J = 7.6	7.90 (d) J = 8.1
2g	m-CF$_3$-C$_6$H$_4$ 7.56 (t), 1H, J = 7.6; 7.67 (d), 1H, J = 8.0 7.93 (d), 1H, J = 8.0; 8.44 (s), 1H	7.08 (s)	CH$_3$ 3.00 (s) 3H	8.35 (d) J = 8.1	7.28 (t) J = 7.6	7.49 (t) J = 7.6	7.91 (d) J = 8.1
3g	CH$_3$ 2.65 (s) 3H	6.62 (s)	m-CF$_3$-C$_6$H$_4$ 7.70-8.10 (m) 4H	6.55 (d) J = 8.1	7.00 (t) J = 7.6	7.41 (t) J = 7.6	7.80 (d) J = 8.1
3k	CH$_3$ 2.67 (s) 3H	6.52 (s)	C$_6$H$_5$ 7.56 (bs) 5H	6.55 (d) J = 8.1	6.95 (t) J = 7.6	7.34 (t) J = 7.6	7.85 (d) J = 8.1
3ℓ	C$_6$H$_5$ 7.32-7.57 (m), 3H, 8.05-8.30 (m), 2H	7.17 (s)	m-CF$_3$-C$_6$H$_4$ 7.75-8.10 (m) 4H	6.52 (d) J = 8.1	6.97 (t) J = 7.6	7.35 (t) J = 7.6	7.85 (d) J = 8.1
3q	C$_6$H$_5$ 7.35-7.55 (m), 3H, 8.15-8.40 (m), 2H	7.20 (s)	C$_6$H$_5$ 7.62 (bs) 5H	6.62 (d) J = 8.1	6.97 (t) J = 7.6	7.35 (t) J = 7.6	7.90 (t) J = 8.1

[a] Spectra were taken in deuteriochloroform solutions on a Varian Associates FT-80 Spectrometer with tetramethylsilane as the internal standard. Coupling constants are in hertz (Hz) and chemical shifts values are in δ (ppm) units. Multiplicity = d, doublet; m, multiplet; t, triplet; s, singlet; bs, broadened singlet.

Structure assignments for **2** and **3** were made on the basis of ^{1}H nmr spectroscopy. For example, the ^{1}H nmr spectrum of **2a** showed a shift of one proton downfield to 8.47 ppm from the multiplet containing the other three benzene protons in the pyrimido[1,2-a]benzimidazole nucleus. This proton is assigned as 6-H in agreement with the deshielding effect observed in similar "angular" proton interactions [11]. The other three aromatic protons 7-H, 8-H and 9-H showed the expected chemical shifts and couplings in the 7.44 to 7.90 ppm region (Table III). The two pairs of doublets at 7.44 and 8.82 ppm with a coupling of 7.2 Hz are due to 3-H and 4-H respectively. This coupling constant is typical for protons attached to a π-bonded carbon. The large downfield shift for 4-H is also indicative of the deshielding effect of the angular proton interaction. In **2g**, the proton signal for 3-H became a singlet at 7.08 ppm due to the substitution of the 4-H by a methyl group, and the nmr signal for the methyl protons appeared at 3.00 ppm as a singlet. The ^{1}H nmr spectrum of **3a** was quite different from that of **2a**; the proton signal of 6-H shifted upfield very significantly to 6.73 ppm indicating that it was highly shielded. Dreiding molecular models showed that the plane of the m-CF$_3$ phenyl group, substituted at the 4-position, must be oriented out of the plane of the pyrimido[1,2-a]benzimidazole nucleus in order to prevent unfavorable steric interaction with the 6-H hydrogen. Consequently, the 6-H was situated above or below the plane of the m-CF$_3$ phenyl group and was shielded by the ring current effect.

This shielding effect was also observed for 7-H in which its proton signal shifted from 7.44 ppm in **2a** to 7.09 ppm in **3a**. Other evidence for the structure of the regioisomer **3a** is the lower coupling constant of 4.1 Hz for 2-H and 3-H indicating that both protons are attached to a σ-bond. These data, as well as the larger coupling constant of 7.5 Hz for 3-H and 4-H in **2a**, are consistent with the spectral data reported for the parent pyrimido[1,2-a]benzimidazole [12]. Similar spectral features distinctive for the regioisomers **2** and **3** were observed for all compounds listed in Table II. Some additional examples of typical ^{1}H nmr spectral data are also recorded in Table III. The determination of the position of the phenyl group substitution on the pyrimido[1,2-a]benzimidazole ring, especially in **3ℓ**, was further made by comparing the ^{1}H nmr pattern of the aromatic protons. In **2a**, **2f** and **2g**, in which the m-CF$_3$ phenyl or phenyl group is substituted at the 2-position, the proton signals showed more distinctive chemical shifts and couplings indicating conjugation of the phenyl ring with the pyrimido[1,2-a]benzimidazole nucleus. In **3a**, **3f** and **3g**, where the m-CF$_3$ or phenyl group is substituted at the 4-position, the aromatic protons appeared as undefined multiplets or as a broad singlet in the 7.50-8.10 ppm region. This can be attributed to the noncoplanarity of the phenyl ring with the pyrimido[1,2-a]benzimidazole ring. The uv spectral data of **2** and **3** also support this conclusion (Table IV). In **2**, the two absorption maxima caused by the π-π* transitions appeared at about 332 and 270

nm. However, in **3**, these maxima were shifted to the shorter wavelength region at about 320 and 250 nm. This suggests that the phenyl group at the 2-position in **2** achieved coplanarity more readily with the pyrimido[1,2-a]benzimidazole ring thus allowing a higher degree of overlap in the π electron system. In **3**, since the phenyl group is substituted at the 4-position, its rotation is hindered by the steric interaction with 6-H; coplanarity with the pyrimido-[1,2-a]benzimidazole ring is restricted and the length of the π electron system is effectively reduced. The difference in the extinction coefficients in the 315-335 nm region between **2** and **3** also shows this steric effect.

The ring closure reaction between 2-aminobenzimidazoles and enaminones in acetic acid probably proceeds by two pathways. The first pathway involves the usual condensation between ketone and amine to form a Schiff base **A**, which then cyclizes to form **2**. The second pathway involves an initial Michael-type addition of the nucleophilic amino group in the benzimidazole to the enaminone, followed by the elimination of the dimethylamino group. The intermediate **B** then cyclizes to form **B-1** with subsequent dehydration to give **3**.
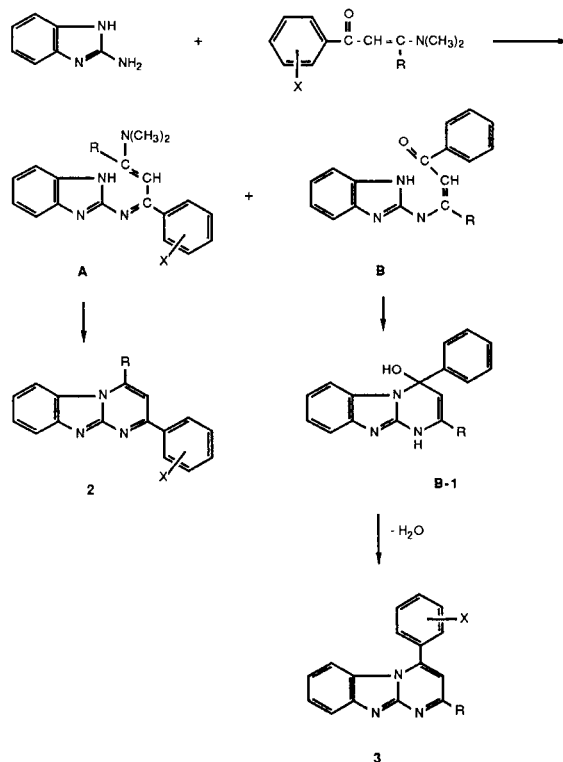
Table IV

UV Spectral Data of Some
Pyrimido[1,2-a]benzimidazoles [a]

Compound Number	λ max nm	ε
2a	334	15086
	267	39563
3a	321	3411
	248	21421
2f	331	12911
	272	32344
3f	320	5532
	249	33481
2g	329	12546
	267	37248
3g	318	5869
	250	34073
3k	315	5694
	250	37764
3l	341	14801
	274	35103
3q	340	17038
	274	42603

[a] Spectra were taken in methanol.

When the R group in enaminone **1** is either a methyl or a phenyl group, the cyclization of **A**, leading to **2**, would be less favored due to the steric hinderence of these groups. Thus, the major or the only cyclization that takes place would be by way of intermediate **B**; the addition-elimination pathway similar to the formation of the interme-

Table V

Analytical Data of All Compounds Reported

| Compound Number	C Calcd. (Found)	H Calcd. (Found)	N Calcd. (Found)	X (Cl or F) Calcd. (Found)
1a	59.26 (59.17)	4.94 (4.97)	5.76 (5.64)	23.46 (23.30)
1b	63.01 (62.94)	5.73 (5.69)	6.68 (6.75)	16.95 (17.04)
1c	63.01 (63.18)	5.73 (5.64)	6.68 (6.65)	16.95 (16.89)
1d	76.19 (76.05)	7.94 (7.88)	7.41 (7.52)	
1e	70.24 (69.98)	7.32 (7.15)	6.83 (6.95)	
1f	75.43 (75.39)	7.43 (7.47)	9.79 (9.65)	
1g	60.70 (60.76)	5.45 (5.35)	5.45 (5.30)	22.18 (22.19)
1h	64.43 (64.23)	6.26 (6.15)	6.26 (6.38)	15.88 (15.95)
1i	64.43 (64.60)	6.26 (6.21)	6.26 (6.33)	15.88 (15.79)
1j	76.85 (76.95)	8.37 (8.33)	6.90 (6.95)	
1k	76.19 (76.05)	7.94 (7.88)	7.41 (7.58)	
1ℓ	67.71 (68.06)	5.02 (5.15)	4.39 (4.63)	17.87 (17.65)
1m	71.45 (71.52)	5.60 (5.62)	4.90 (4.80)	12.43 (12.26)
1n	71.45 (71.68)	5.60 (5.87)	4.90 (4.99)	12.43 (12.12)
1o	81.51 (81.68)	7.17 (7.44)	5.28 (5.20)	
1p	76.87 (76.56)	6.76 (6.82)	4.98 (4.87)	
1q	79.38 (79.61)	6.61 (6.96)	5.45 (5.65)	
2a	65.18 (64.93)	3.22 (3.39)	13.41 (13.14)	18.19 (18.03)
3a	65.18 (65.31)	3.22 (3.31)	13.41 (13.18)	18.19 (17.93)
2b	68.70 (68.61)	3.60 (3.63)	15.02 (14.83)	12.67 (12.81)
3b	68.70 (68.59)	3.60 (3.61)	15.02 (14.91)	12.67 (12.66)
3c	68.70 (68.60)	3.60 (3.45)	15.02 (14.85)	12.67 (12.79)
2d	78.74 (78.66)	5.05 (5.19)	16.02 (16.44)	
3d	78.74 (78.88)	5.05 (5.09)	16.20 (15.93)	
2e	72.99 (73.29)	4.98 (4.70)	15.96 (15.79)	

Table V (continued)

Compound Number	C Calcd. (Found)	H Calcd. (Found)	N Calcd. (Found)	X (Cl or F) Calcd. (Found)
3e	72.99 (73.17)	4.98 (4.78)	15.96 (15.88)	
2f	78.35 (78.21)	4.52 (4.65)	17.13 (17.10)	
3f	78.35 (78.27)	4.52 (4.69)	17.13 (17.23)	
2g	66.05 (65.90)	3.70 (3.61)	12.84 (12.70)	17.41 (17.45)
3g	66.05 (65.84)	3.70 (3.55)	12.84 (12.60)	17.41 (17.43)
2h	69.51 (69.31)	4.12 (3.89)	14.30 (14.08)	12.07 (12.05)
3h	69.51 (69.39)	4.12 (4.01)	14.30 (14.12)	12.07 (12.18)
3i	69.51 (69.79)	4.12 (3.98)	14.30 (14.34)	12.07 (11.96)
2j	79.10 (78.91)	5.53 (5.47)	15.37 (15.41)	
3j	79.10 (78.85)	5.53 (5.39)	15.37 (15.17)	
3k	78.74 (78.68)	5.05 (5.08)	16.20 (16.36)	
3ℓ	70.95 (70.73)	3.62 (3.65)	10.79 (10.75)	14.64 (14.45)
3m	74.26 (74.03)	3.97 (3.87)	11.81 (11.89)	9.96 (9.83)
3n	74.26 (73.98)	3.97 (3.75)	11.81 (11.65)	9.96 (9.79)
3o	82.61 (82.49)	4.82 (5.01)	12.57 (12.60)	
3p	78.61 (78.50)	4.88 (4.75)	11.96 (12.10)	
3q	82.22 (82.22)	4.67 (4.80)	13.08 (13.02)	

diate **B** has been proposed to explain the formation of 1,4-dihydro-4-oxopyrimido[1,2-a]benzimidazole-3-carbonitrile from the reaction of 2-aminobenzimidazole with ethoxymethylenecyanoacetate [13,14].
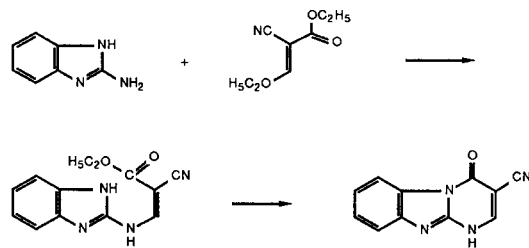
Our present results demonstrate the use of enaminones as versatile synthons in a simple synthesis of pyrimido-[1,2-a]benzimidazoles. The most significant observation is the regioselectivity of the condensation reaction between 2-aminobenzimidazole and enaminone 1 when R in 1 is a methyl or a phenyl group. This stereo-controlled cyclization of enaminones with 2-aminobenzimidazole is believed to be the first example ever reported. Further work is in progress to explore the utility of the versatile synthons in the regioselective synthesis of other novel heterocycles.

EXPERIMENTAL

All melting points were determined with a Mel-Temp apparatus and are uncorrected. Microanalyses were carried out by the Analytical Services Section of Lederle Laboratories. All ^{1}H nmr chemical shifts are reported in δ (ppm) units downfield from tetramethylsilane and are measured in deuteriated chloroform on a Varian Associates FT-80 spectrometer. The coupling constants are recorded in Hz units. Ultraviolet spectra were taken on a Hewlett Packard 8450A spectrophotometer, ir spectra were recorded on a Nicolet 7199 FT-IR Spectrophotometer and samples were prepared as mulls in potassium bromide pellets. Mass spectra were recorded on a Varian MAT CH7 Mass Spectrometer using electron impact mode. Preparative hplc was carried out with a Waters Prep LC/system 500A equipped with a refractive index detector. For the flash column chromatography, Davisil 62 silica gel was used. Thin-layer chromatography was performed with Analtech Silica Gel GF plates and the spots were visualized by a Mineralight UVGL-25 lamp.

General Synthesis of Enaminones 1.

N,N-Dimethylformamide dimethyl acetal was purchased from Burdick & Jackson Laboratories, N,N-dimethylacetamide dimethyl acetal was purchased from Fluka Chemical Corp. N,N-Dimethylbenzamide diethyl acetal was prepared according to the procedure of Parker et al. [5].

Example A. 3-Dimethylamino-3-(trifluoromethyl)acrylophenone (1a).

A mixture of m-trifluoromethylacetophenone (14 g, 74 mmoles) and dimethylformamide dimethyl acetal (20 ml) was heated at 120° for 2 hours. The mixture was then evaporated on a rotary evaporator to give a thick oil which crystallized on cooling. The yellow crystals were washed with hexane, collected by filtration and then dried (14.3 g, 80%); uv (methanol): 241 (ε 10699) and 346 nm (18990); ir: 1640, 1600, 1560, 1330 cm^{-1}; ^{1}H nmr: δ 3.0 (s, 6H), 5.5 (s, 1H), 5.8 (s, 1H), 7.3-8.15 (m, 4H); ms: m/e 243 (M$^+$).

Example B. 3-(Dimethylamino)-1-[3-trifluoromethyl-phenyl]-2-buten-1-one (1g).

A mixture of m-trifluoromethylacetophenone (15 g, 80 mmoles) and N,N-dimethylacetamide diethyl acetal (25 ml) was heated at 120° for 3 hours. The mixture was then evaporated on a rotary evaporator to give a thick oil which solidified upon standing. It was washed with hexane and collected by filtration and dried (18 g, 88%); uv (methanol): 238 (ε 10424) and 342 nm (24079); ir: 1640, 1600, 1560, 1330 cm^{-1}; ^{1}H nmr: δ 2.85 (s, 3H), 3.25 (s, 6H), 5.70 (s, 1H), 7.5-8.3 (m, 4H); ms: m/e 257 (M$^+$).

Example C. 3-(Dimethylamino)-3-phenyl-1-[3-(trifluoromethyl)phenyl]2-propen-1-one (1l).

A mixture of m-trifluoromethylacetophenone (8 g, 42.6 mmoles) and N,N-dimethylbenzamide diethyl acetal (12 g, 54 mmoles) in dry toluene (20 ml) was heated at 120° for 40 hours. The mixture was evaporated on a rotary evaporator to remove toluene and low boiling liquid. The residue was then distilled through a Kugelrohr apparatus to obtain the desired enaminone (4.5 g, 33%); uv (methanol): 238 (ε 8749) and 349 nm (1200); ir (neat): 1630, 1600, 1530, 1400, 1330 cm^{-1}; ^{1}H nmr: δ 3.0 (s, 6H), 5.9 (s, 1H), and 7.6-8.3 (m, 4H); ms: m/e 319 (M$^+$).

General Synthesis of pyrimido[1,2-a]benzimidazoles.

Example D. 2-[3-(Trifluoromethyl)phenyl]pyrimido[1,2-a]benzimidazole (2a) and 4-[3-(Trifluoromethyl)phenyl]pyrimido[1,2-a]benzimidazole (3a).

A mixture of 2-aminobenzimidazole (6.65 g, 50 mmoles), 3-dimethylamino-3-(trifluoromethyl)acrylphenone (1a, 12.15 g, 50 mmoles) and glacial acetic acid (50 ml) was refluxed for 4 hours and then evaporated on a rotary evaporator to give a thick oil. On cooling, methylene chloride was added to this thick oil and the resulting solution was neutralized with a saturated solution of sodium bicarbonate. The yellow precipitate which formed from the two-layer solution was filtered and washed with water, then dried to give 2.21 g of the product 2a, tlc R$_f$, 0.67 (ethyl acetate); ir (potassium bromide): 1630, 1600, 1520, 1460, 1340 cm^{-1}; ms: m/e 313 (M$^+$).

The methylene chloride layer was separated from the filtrate and was dried over sodium sulfate. Evaporation of the solvent gave a gummy material which was triturated with ether to form a yellow solid (5 g). Tlc of this solid showed two yellow fluorescent spots (R$_f$, 0.67 and 0.29, ethyl acetate). The mixture was separated by preparative hplc (ethyl acetate:hexane, 2:1) to give an additional 0.9 g of 2a and 3.11 g of 3a, tlc R$_f$ of 3a, 0.29 (ethyl acetate); ir: 1630, 1600, 1520, 1460, 1340 cm^{-1}; ms: m/e 313 (M$^+$).

Example E. 4-Methyl-2-[3-(trifluoromethyl)phenyl]pyrimido[1,2-a]benzimidazole (2g) and 2-Methyl-4-[3-(trifluoromethyl)phenyl]pyrimido[1,2-a]benzimidazole (3g).

A mixture of 2-aminobenzimidazole (6.65 g 50 mmoles), 3-(dimethylamino)-1-[3-trifluoromethylphenyl]-2-buten-1-one (1g) (13 g, 0.05 mole) in glacial acetic acid (80 ml) was heated to reflux for 5 hours then evaporated on a rotary evaporator to give a thick oil. This thick oil was dissolved in methylene chloride and neutralized with a saturated solution of sodium bicarbonate. The methylene chloride layer which separated was passed through a layer of Magnesol (synthetic hydrous magnesium silicate) and was further dried over sodium sulfate. Evaporation of the solvent gave a semi-solid which was triturated with ethyl acetate to give 5.5 g of yellow crystals identified as 3g; tlc R$_f$, 0.60 (ethyl acetate); ir (potassium bromide): 1630, 1600, 1530, 1440, 1320 cm^{-1}; ms: m/e 327 (M$^+$).

The ethyl acetate filtrate was evaporated to dryness and then triturated with ether to give 3.6 g of a yellow precipitate. Tlc (ethyl acetate) showed two yellow fluorescent spots (R$_f$, 0.26 and 0.60). This mixture was then separated by preparative hplc (ethyl acetate:hexane, 1:2) to give additional 3.06 g of 3g and 0.18 g of 2g, tlc R$_f$ of 2g, 0.26; ir (potassium bromide): 1630, 1600, 1530, 1440, 1320 cm^{-1}; ms: m/e 327 (M$^+$).

Example F. 2-Phenyl-4-[3-(trifluoromethyl)phenyl]pyrimido[1,2-a]benzimadazole (3l).

A mixture of 2-aminobenzimidazole (1.9 g, 14.3 mmoles), 3-(dimethylamino)-3-phenyl-1-[3-(trifluoromethyl)phenyl]-2-propen-1-one (1l) (4.4 g, 14.5 mmoles) and glacial acetic acid (40 ml) was heated at reflux for 18 hours and then evaporated on a rotary evaporator to give a semi-solid which was dissolved in methylene chloride, and this solution was neutralized with a saturated solution of sodium bicarbonate. The methylene chloride layer was separated, dried over sodium sulfate and filtered. Evaporation of the solvent gave a yellow solid which was washed with hexane and dried to give 2.8 g of 3l. It was further recrystallized from ethyl acetate, tlc R$_f$, 0.82 (ethyl acetate); ir: 1640, 1620, 1530, 1450, 1330 cm^{-1}; ms: m/e 389 (M$^+$).

REFERENCES AND NOTES

[1] G. Tennant in "Heterocyclic Chemistry", Vol **40**, P. N. Preston, ed, John Wiley and Sons, Inc., New York, NY, 1980, p 257.

[2] W. Reid and W. Muller, *J. Prakt. Chem.*, **8**, 132 (1959).

[3] L. Basaglia and B. Mariani, *Ann. Chim.* (Rome), **53**, 755 (1963).

[4] A. Kreutzberger and M. Leger, *Arch. Pharm.* (Weinheim), **315**, 47 (1982).

[5] K. A. Parker, J. J. Petraitis, R. W. Kosley, Jr., and S. L. Buchwald, *J. Org. Chem.*, **47**, 389 (1982).

[6] H. Bredereck, F. Effenberger, H. Botsch and H. Rehn, *Chem. Ber.*, **98**, 1081 (1965).

[7] H. Bredereck, G. Simchen and W. Griebenow, *Chem. Ber.*, **107**, 1545 (1974).

[8] J. V. Greenhill, *Chem. Soc. Rev.*, **6**, 277 (1977).

[9] R. F. Abdulla and R. S. Brinkmyer, *Tetrahedron*, 1675 (1979).

[10] J. P. Dusza, private communication, Medical Research Division, American Cyanamid Company, Pearl River, NY.

[11] W. W. Paudler and T. J. Kress, *J. Org. Chem.*, **32**, 2616 (1967).

[12] L. M. Werbel, A. Curry, E. F. Elslager, C. A. Hess, M. P. Hutt and C. Youngstrom *J. Heterocyclic Chem.*, **6**, 787 (1969).

[13] A. W. Chow, D. R. Jakas, B. P. Trotter, N. M. Hall and J. R. E. Hoover, *J. Heterocyclic Chem.*, **10**, 71 (1973).

[14] K. D. Kampe, *Angew. Chem., Int. Ed. Engl.*, **21**, 540 (1982).