HETEROCYCLES, Vol. 78, No. 3, 2009, pp. 691 - 698. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd September, 2008, Accepted, 17th November, 2008, Published online, 17th November, 2008
DOI: 10.3987/COM-08-11558

SYNTHESIS OF NITROGEN-CONTAINING HETEROCYCLES 12. REACTIONS OF 2-AMINO-1-BENZYLIDENEAMINO-1*H*-IMIDAZOLES WITH DIMETHYL ACETYLENEDICARBOXYLATE

Yoshiko Miyamoto

Department of Chemistry, Kitasato University of Japan, 1-15-1 Kitasato, Sagamihara, Kanagawa 228-8555 Japan, e-mail: yoshiko@sci.kitasato-u.ac.jp

Abstract – 2-Amino-4-aryl-1-benzylideneamino-1*H*-imidazoles **(1)** reacted with dimethyl acetylenedicarboxylate (DMAD) in benzene to give dimethyl 2-amino-1-benzylidene-amino-1*H*-pyrrole-3,4-dicarboxylates **(3)**, benzonitriles **(4)** and dimethyl 1-(2-amino-1-benzylideneamino-4-aryl-1*H*-imidazole-5-yl)fumarates **(5)** in moderate to high yields. Compounds **3** and **4** were considered as the reaction products of the intermediary Diels-Alder adducts, dimethyl 1-amino-3-aryl-7-benzylideneamino-2,7-diazabicylo[2.2.1]hepta-2,5-diene-5,6-dicarboxylates **(2)**, which were not isolated and decomposed in a retro Diels-Alder reaction. The products **5** resulted from a Michael conjugate addition reaction of **1** to DMAD.

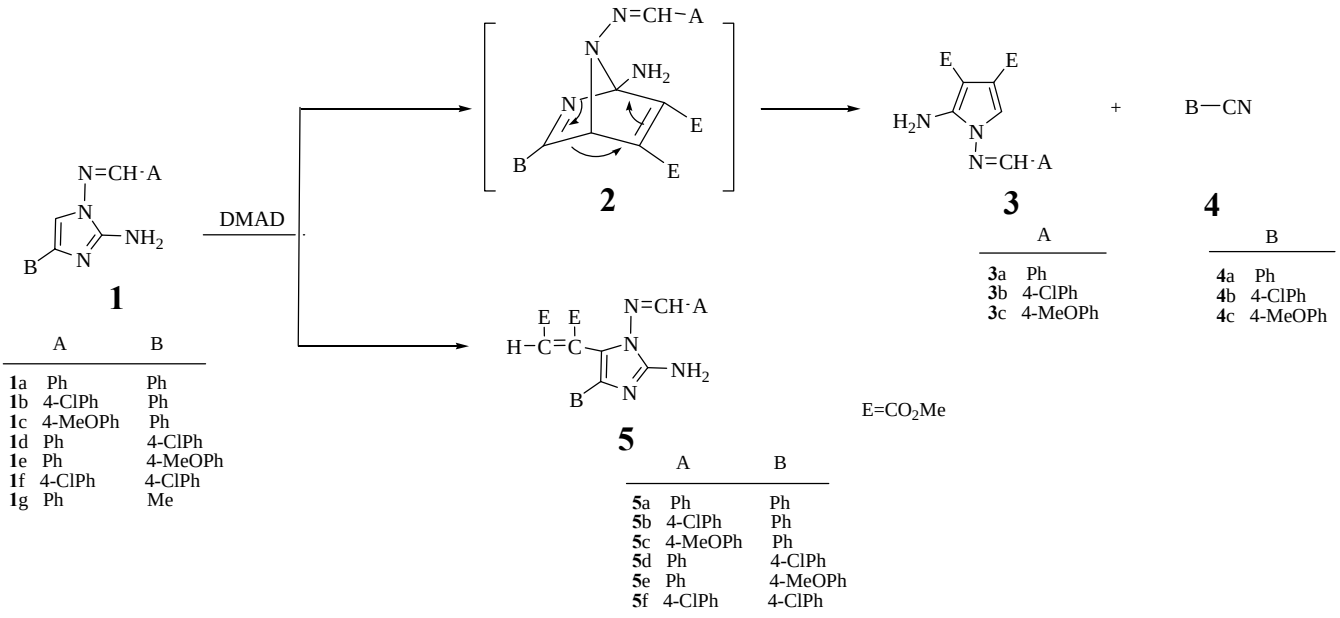
INTRODUCTION

In previous publications bicyclic 1-benzylideneamino-6-cyano-5-imino-1*H*-imidazo[1,2-*a*]pyrimidines have been derived from 2-amino-1-benzylideneamino-1*H*-imidazoles **(1)** and ethoxymethylenemalonitrile.[1] Reaction of 2-amino-1-methylimidazole with dimethyl acetylenedicarboxylate (DMAD) has also been reported to afford methyl 1-methyl-5-oxo-1*H*-imidazo[1,2-*a*]pyrimidin-7-carboxylate and dimethyl 2-amino-2-methyl-1*H*-1,3-diazepine-5,6-dicarboxylate.[2] Analogous to Troxler *et al.*,[2] reactions of 2-amino-4-aryl-1-benzylideneamino-1*H*-imidazoles **(1)** with DMAD have been studied. Thus, it was found that **(1)** gave dimethyl 2-amino-1-benzylideneamino-1*H*-pyrrole-3,4-dicarboxylates **(3)**, benzonitriles **(4)** and dimethyl 2-(2-amino-1-benzylideneamino-4-aryl-1*H*-imidazol-5-yl)fumarates **(5)** in moderate to high yields instead of the expected imidazopyrimidines. Formation of products **3** and **4** may be considered as results of the *retro*-decomposition of the Diels-Alder adducts of **1** and DMAD. Formations of **5** resulted from a Michael type of conjugate addition of imidazoles **(1)** to DMAD.

Generally, diene systems present in oxazole derivatives have been well known to undergo Diels-Alder cycloaddition[3,4] and also the retro-decomposition of the adducts. The strongly electron-negative oxygen in the oxazole ring brings about low aromaticity indices (I_A 47),[5] indicating more favorable contribution for the Diels-Alder cycloaddition. But aromaticity indices of imidazole derivatives are higher (I_A79), presupposing poorer formation of Diels-Alder adducts.[6] Formation of dimethyl 2-merucapto-1-benzylideneamino-1*H*-pyrrole-3,4-dicarboxylates and benzonitriles from 4-aryl-1-benzylideneamino-2-mercapto-1*H*-imidazoles and DMAD in boiling chlorobenzene and the proposed structure of the intermediate Diels-Alder cycloaddact have been already reported.[7] But this author has failed in reacting 1-benzylideneamino-2-amino-4-phenyl-1*H*-imidazole with DMAD. Formation of pyrroles **(3)** and benzonitriles **(4)** in this paper may provide an example that 1-benzylideneamino-2-amino-4-aryl-1*H*-imidazoles **(1)** are utilized also in Diels-Alder reaction.

RESULTS AND DISCUSSION

The reaction of 2-amino-4-aryl-1-bemzylideneamino-1*H*-imidazoles (**1a-1f**) with dimehyl acetylenedicarboxylate (DMAD) was carried out in refluxing benzene for 10 min. Chromatographic separation gave dimethyl 2-amino-1-benzylideneamino-1*H*-pyrrole-3,4- dicarboxylates (**3a-3c**), benzonitriles (**4a-4c**) and dimethyl 2-(2-amino-1-benzylideneamino-4-aryl-1*H*-imidazole-5-yl)fumatates (**5a-5f**) in moderate to high yields (see Scheme 1 and Table 1).



Scheme 1

Table 1. Yields of the synthesized compounds

starting material	A	B	product **3** (yield %)	product **4** (yield %)	product **5** (yield %)
1a	Ph	Ph	**3a** (31)	**4a** (27)	**5a** (36)
1b	4-ClPh	Ph	**3b** (68)	**4a** (30)	**5b** (23)
1c	4-MeOPh	Ph	**3c** (22)	**4a** (7)	**5c** (15)
1d	Ph	4-ClPh	**3a** (33)	**4b** (33)	**5d** (34)
1e	Ph	4-MeOPh	**3a** (25)	**4c** (10)	**5e** (35)
1f	4-ClPh	4-ClPh	**3b** (73)	**4b** (36)	**5f** (7)

1. Structure confirmation of reaction products

Structures of products **3a**, **3b** and **3c** were confirmed through ^{1}H NMR , ^{13}C NMR and mass spectra, as mentioned below. The resonances of the four ring carbons in the 2-aminopyrrol (**3a)** appeared at δ_C 89.66 as a doublet ($^{3}J_{CH}$=5.8 Hz), δ_C 110.4 as a doublet ($^{1}J_{CH}$=194 Hz), δ_C 114.0 as a doublet ($^{2}J_{CH}$=4.1 Hz) and δ_C 146.8 as doublet ($^{3}J_{CH}$=6.6 Hz), and were easily assigned to C-3, C-5, C-4 and C-2 respectively. The N=CH carbon resonance of 1-benylideneamino group appeared at δ_C 148.5 as doublet with coupling constant ($^{1}J_{CH}$=161 Hz). In ^{1}H nmr spectra, the amino group at the pyrrole ring resonated in a single signal of two-proton intensities at **δ**5.78 and the ring proton signal of C-5 of pyrrole appeared at **δ**7.30 as a singlet. NMR-data of **3b** and **3c** were shown also in Table 2. In the mass spectra, molecular ions were obtained for pyrroles **(3)** with intensity (46-100%).

Table 2. 2-Amino-1-arylmethyleneamino-1*H*-pyrrole-3,4-dicarboxylate derivatives **3**

		^{1}H nmr		^{13}C nmr (J values in Hz)		MS (Rel. Int)		
No.	Mp(°C)	N=CH	C-5	N=CH	C-5	M^+	m/e 197	m/e 166
3a	156-157	8.28	7.30	148.5(161)	110.4(194)	301(100),	M^+-104 (44),	M^+-135 (95)
3b	152-153	8.27	7.25	147.0(160)	110.1(194)	335(46),	M^+-138 (44),	M^+-169 (100)
3c	117-120	8.24	7.29	148.6(160)	110.7(194)	331(88),	M^+-134 (30),	M^+-165 (100)

Structure of compound **3a** was confirmed also by an X-ray structural analysis (see Figure 1).

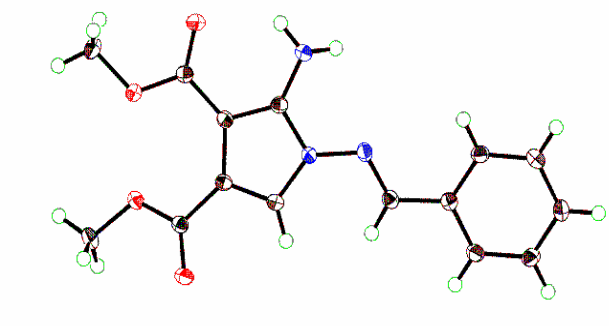


Figure 1. Structure of compound **3a**

The structures of the benzonitriles (**4a-4c),** were confirmed by spectroscopic data (see Experimental).

In the series of products **5** dimethyl 2-(2-amino-1-benzylideneamino-4-aryl-1*H*-imidazole- 5-yl)fumarates (**5a-5f**) show the ring carbon signals of C-2, C-4 and C-5 of the imidazole ring (**5a-5f**) at **δ** 141.7-142.1 as a singlet, **δ**135.7-138.6 as a singlet and **δ**113.0-113.0 as a singlet, respectively.

In the ^{1}H nmr spectra, the amino group at the imidazole ring resonated in a single signal of two proton intensities in the region of **δ**4.78-5.47 as singlet. In the mass spectra, molecular ions were obtained for compounds **5a-5f** with intensity (34-100%). The fragment ions, A-CN and A-CN^{+}H, observed in the spectra of 1*H*-imidazole dicarboxylates **5a-5f** were characteristic of the imidazole structure (see Table 3). Structure of **5a** was confirmed also by X-ray structural analysis.

Table 3. Dimethyl 1-(2-amino-1-benzylideneamino-4-aryl-1*H*-imidazole-5-yl)fumarates(**5)**

		^{1}H nmr		^{13}C nmr (J values in Hz)		MS m/z (Rel. Int)				
No.	Mp(ºC)	N=CH	C=CH	N=CH(d)	C=CH(d)	M^{+}	base peak	A-CN	A-CN^{+}H	165
5a	155-156	8.39	6.02	149.2(161).	121.6(168)	404(40),	103	103(100),	104(46),	M^{+}-239(26)
5b	180-181	8.40	6.04	148.6(160),	122.7(168)	438(100),	438	137(69),	138(66),	M^{+}-273(60)
5c	167-169	8.32	6.01	149.0(160),	121.1(168)	434 (70),	134	133(50),	134(100),	M^{+}-269(60)
5d	168-170	8.17	6.90	148.1(160),	121.0(168)	438 (83),	165	103(10),	104(13),	M^{+}-273(100)
5e	161-162	8.39	6.01	148.5(160),	120.3(168)	434(90),	104	103(65),	104(100),	M^{+}-269(100)
5f	194-196	8.13	6.89	148.6(160),	121.2(168)	472(34),	165	137(30),	138(34),	M^{+}-307(100)

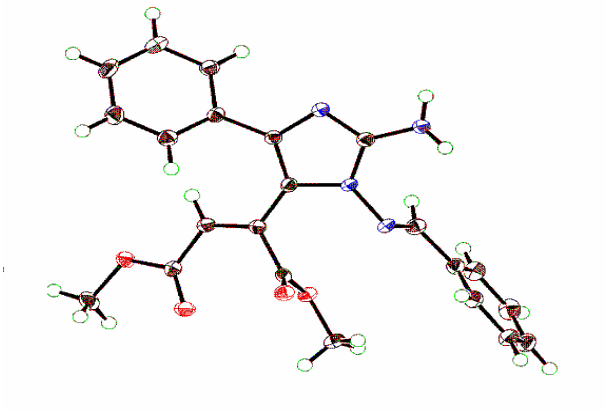
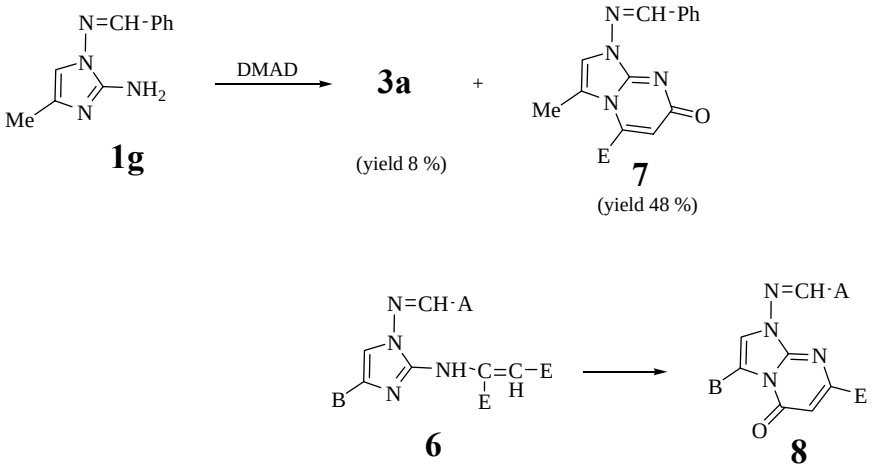


Figure 2. X-Ray structure of compound **5a**

The isomers of configuration around C=C double bond of **5** is a E-form from the X-ray structural analysis (see Figure 2).

When the reaction of 4-methylimidazole **(1g)** with DMAD was carried out under the same condition, pyrrole (**3a)** and imidazo[1,2-*a*]pyrimidine **(7)** were obtained, whereas no Michael type adduct was detected in the reaction mixture. Structure of compound **7** was confirmed by X-ray structural analysis.



Scheme 2

2. Aspect of the reaction of 2-amino-4-aryl-1-benzylidene-amino-1H-imidazoles (1) with dimehyl acetylene dicarboxylate (DMAD)

After reaction, neither enamines **(6)** nor imidazo[1,2-*a*]pyrimidine **(8)** were detected in the products (see structures of **6** and **8**, in Scheme 2). Only three products, dimethyl 2-amino-1-benzylideneamino-1*H*-pyrrole-3,4-dicarboxylates **(3)**, benzonitriles **(4)** and dimethyl 2-(2-amino-1-benzylideneamino-4-aryl-1*H*-imidazol-5-yl)fumarates **(5),** were found in reaction mixtures. Formation of pyrroles **(3)** and benzonitriles **(4)** may be readily elucidated by retro decomposition of Diels-Alder adducts, dimethyl 1-amino-7-(benzylideneamino)-3-aryl-2,7-diazabicylo[2,2,1]-hepta-2,5-diene-5,6-dicarboxylates **(2),** which were not isolated in the reactions. Namely, the [4+2]-cycloadducts **(2)** formed in intermolecular pericyclic processes rapidly liberate benzonitriles **(4)** to produce pyrroles **(3)** in retro Diels-Alder reaction. Since the starting imidazoles (**1a**, **1d** and **1e**) yielded the same pyrrole (**3a**) as well as the starting (**1b** and **1f**) gave the same pyrrole (**3b**), the decomposing mechanism is quite accurate. Comparing the yields of pyrrole (**3a**) with other pyrrole products (**3b and 3c**) show that the introduction of an electron-withdrawing chlorine atom on the benzene ring of 1-benzylidene-amino group of the imidazole (**1a**) increase the yield of pyrrole (**3b**), whereas introduction of an electron-donating methoxy group gave a little decrease on the yield of pyrrole (**3c**). The best yield of pyrrole **(3b)** was obtained when 2-amino-1-(4-chlorobenzylidene-amino)-4-(4-chlorophenyl)-1*H*-imidazoles (**1f**) reacted with **DMAD,** although introduction of a chlorine atom or a methoxy group in the benzene ring of the 4-phenyl group (**1a**) gave little or no effect on the yield of pyrrole (**3a**). Introduction of electron-withdrawing groups at the benzene ring of 1-benzylidene-amino group may enhance the conjugate diene character of the aza-dienes suited for Diels-Alder cycloaddition.

On the other hand, dimethyl 2-(2-amino-1-benzylideneamino-4-aryl-1*H*-imidazol-5-yl)fumarates **(5)** are

considered as a type of Michael adduct of imidazoles **(1)** to DMAD.

Since the reaction selectivity of the products (pyrrole **(3a)**/Michael adduct **(5a)**) is almost 1:1, an electron-withdrawing chlorine atom at the benzene ring of 1-benzylideneamino group of the imidazole (**1a**) increases the yield of pyrrole (**3b**), indicating higher selectivity of pyrrole (**3b**) and priority of Diels-Alder cycloaddition.

The reaction of imidazole (**1a**) with DMAD was carried out in benzene at rt for 1h, giving 15% yield of **3a** and 53% yield of **5a** indicating a preference of the Michael adduct (**5a**).

Reaction of 2-amino-1-benzylideneamino-4-methyl-1*H*-imidazole (**1g**) yielded a small amount (8% yield) of dimethyl 2-amino-benzylideneamino-1*H*-pyrrole-3,4-dicarboxyate (**3a**) and methyl 1-benzylideneamino-4-methyl-7-oxo-1H-imidazo[1,2-*a*]pyrimidin-5-carboxylate (**7**) (48%) like Troxler type's condensation product, but no Michael adduct **5**. However, the structure of **7** was different from methyl 1-benzylideneamino-4-methyl-5-oxo-1*H*-imidazo[1,2-*a*]pyrimidin- 7-carboxylate (**8**), which may be formed *via* an enamine adduct (**6**) of **1g** with DMAD.

Dimethyl 1-benzylideneamino-2-mercapto-1*H*-pyrrole-3,4-dicarbozylates and benzonitrile were produced in the reaction of 2-mercapto-4-aryl-1-benzylideneamino-1*H*-imidazoles with DMAD in boiling chlorobenzene (145-150 ^{o}C, bath temperature).[3] This reaction may proceed also *via* Diels-Alder addition. Since the reaction was not carried out in the milder condition (eg. 80 ^{o}C in CH_3CN), the elevated activation energy was required to start the reaction for 2-mercapto-imidazoles and DMAD, different from the compound **1**.

Two types reaction of Diels-Alder cycloaddition and Michael reaction were confirmed in the reaction of 2-amino-4-aryl-1-benzylideneamino-1*H*-imidazoles (**1**) with DMAD in this paper, the Diels-Alder cycloaddition rapidly was proceeding under refluxing benzene condition, although the Michael reaction was predominant at lower temperature such like rt.

EXPERIMENTAL

Melting points were determined in open capillary tubes and uncorrected. ^{1}H nmr and ^{13}C nmr spectra were obtained with a JNM EX-400 (400 MHz) spectrometer. The chemical shift values were recorded in parts per million (ppm) on the δ scale with tetramethylsilane as the internal reference. The mass spectra (75 eV) were obtained on a JMS-D100 mass spectrometer. The IR spectra were recorded in potassium bromide pellets on a Shimazu FTIR-8400S spectrophotometer.

Trisubstituted imidazole compounds

The starting imidazoles employed were prepared according to the literature,[1,8] some imidazoles, **1e** and **1f,** were new compounds.

2-Amino-1-benzylideneamino-4-(4-methoxyphenyl)-1H-imidazole **(1e)**

A solution of benzaldehyde *N*-aminoguanidinephenylhydrazone (3.24 g, 20 mmol) and 4-methoxyphenacyl bromide (2.29 g, 10 mmol) in EtOH (10 mL) was heated under reflux for 3 h and then evaporated under reduced pressure. The residue was taken up in $CHCl_3$ and the solution was thoroughly washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give substantially pure compound as crystals. Recrystallization from water gave yellow needles (2.04 g, 70%), mp 193-194 ^oC; ^1H nmr (DMSO-d_6): δ 3.83(s, 3H, OMe), 4.92(s, 2H, NH_2), 6.92(d, 2H, J=8.9 Hz, Ph), 7.36(s, 1H, H-5), 7.46(m, 3H, Ph), 7.68(d, 2H, J=8.9 Hz, Ph), 7.80(m, 2H, Ph), 8.14(s, 1H, CH=N); ^{13}C nmr (DMSO-d_6): δ 55.2(q), 98.7(d), 113.9(d), 125.9(d), 126.4(s), 127.5(d), 128.8(d), 130.7(s), 133.1(s), 137.9(s), 145.8(d), 148.5(s), 158.7(s); MS: m/z (relative intensity): 292(M^+, 73), 188(M^+-104, 100); IR (KBr): 3420 (NH_2) cm^{-1}.

Compound **1f** (70%) was obtaind as yellow needles, mp 214-215 ^oC, ^1H nmr (DMSO-d_6): δ 6.33(s, 2H, NH_2), 7.43(d, 2H, J=8.5 Hz, Ph), 7.57(d, 2H, J=8.5 Hz, Ph), 7.74(d, 2H, J=8.5 Hz, Ph), 7.98(d, 2H, J=8.5 Hz, Ph), 8.04(s, 1H, H-5), 8.56(s, 1H, CH=N); ^{13}C nmr (DMSO-d_6): δ 101.8(d), 125.7(d), 128.4(d), 128.9(d), 129.3(d), 130.6(s), 132.5(s), 133.1(s), 135.1(s), 135.6(s), 145.5(d), 149.7(s); MS: m/z (relative intensity): 335(M^++4, 2), 335(M^++2, 10), 331(M^+, 14), 192(M^+-139, 100); IR(KBr): 3427(NH_2) cm^{-1}.

Cycloaddition reaction of 1a with dimethyl but-2-ynedioate (DMAD)

A solution of **1a** (0.26 g, 1.0 mmole) and DMAD (0.17 g, 1.2 mmole) in benzene (7 mL) was heated under reflux for 10 min, and then evaporated under reduced pressure. The residue was subjected to chromatographic separation on silica gel with $CHCl_3$ to give the products **4a** (28 mg), **3a** (93 mg) and **5a** (73 mg) in 27, 31 and 36% yields, respectively.

Benzonitrile (**4a**)

This compound was obtained as an oil; ^1H nmr ($CDCl_3$): δ 7.48(t, 2H, J=7.6 Hz, Ph), 7.61(t, 1H, J=7.6 Hz, Ph), 7.67(d, 2H, J=7.6 Hz, Ph); ^{13}C nmr ($CDCl_3$): δ 115.0(s), 119.1(CN, s), 129.0(d), 132.0(d), 132.6(d); IR (CCl_4): 2208(CN) cm^{-1}.

Dimethyl 2-amino-1-benzylideneamino-1H-pyrrole-3,4-dicarboxylate (**3a**).

This compound was obtained as pale yellow needles, mp 156-157 ^oC; ^1H nmr ($CDCl_3$): δ 3.82(s, 3H, OMe), 3.83(s, 3H, OMe), 5.78(bs, 2H, NH_2), 7.30(s, 1H, 5-H), 7.43(m, 3H, Ph), 7.78(m, 2H, Ph), 8.28(s, 1H, N=CH); ^{13}C nmr ($CDCl_3$): δ 50.9(q), 51.6(q), 89.7(s), 110.4(d), 114.0(s), 128.8(d), 131.5(d), 132.3(s), 146.8(s), 148.5(d), 165.3(s), 164.0(s); MS: m/z (relative intensity): 301(M^+, 100), 166(M^+-135, 78); IR(KBr): 3450, 3350 and 3150(NH_2) and 1722(C=O) cm^{-1}.

Dimethyl 1-(2-amino-1-benzylideneamino-4-phenyl-1H-imidazol-5-yl)fumarate (**5a**)

This compound was obtained as pale yellow needles. mp 155-156 ^{o}C. ^{1}H nmr ($CDCl_3$): δ 3.51(s, 3H, OMe), 3.67(s, 3H, OMe), 4.78(s, 2H, NH2), 6.02(s, 1H, C=CH), 5.47(bs, 2H, NH_2), 7.33(m, 3H, Ph), 7.76(d, 2H, J=8.3 Hz, Ph), 8.39(s, 1H, N=CH); ^{13}C nmr ($CDCl_3$): δ 51.9(q), 52.5(q), 115.0(s), 121.6(s), 127.7(d), 128.1(d), 128.2(d), 128.6(d), 128.8(d), 131.2(d), 131.8(d), 133.5(s), 135.7(s), 142.1(s), 149.2(s), 158.9(s), 165.1(s), 166.3(s); MS: m/z (relative intensity): 404(M^+, 4), 103(M^+-301, 100); IR (KBr): 3368(br, NH_2) and 1700 and 1723(C=O) cm^{-1}.

Cycloaddition reaction of 1g with dimethyl but-2-ynedioate (DMAD)

A solution of **1g** (0.20 g, 1.0 mmole) and DMAD (0.17 g, 1.2 mmole) in benzene (7 mL) was heated under reflex for 10 min, and then evaporated under reduced pressure. The residue was subjected to chromatographic separation on silica gel with $CHCl_3$ to give the products **3a** (25 mg) and **7** (150 mg) in 8.3 and 48% yields, respectively.

1-Benzylideneamino-4-methyl-1H-imidazol-5-oxo-1H-imidazo[1,2-a]pyrimidine-7-carboxylate (**7**)

This compound was obtained as pale yellow fine plates. mp 191-192 ^{o}C. ^{1}H nmr ($CDCl_3$): δ 4.02 (s, 3H, Me), 6.64 (s, 1H, 2-H), 7.06 (s, 1H, H-6), 7.46(m, 3H, Ph), 7.85(m, 2H, Ph), 9.96(s, 1H, CH=N); ^{13}C nmr ($CDCl_3$): 12.0(q), 53.7(q), 114.1(d), 116.7(d), 117.7(s),128.1(d), 128.6(d), 131.4(d), 133.1(s), 135.3(s), 145.3(s), 157.1(s), 161.2(s), 167.9(s); MS: m/z (relative intensity): 310(M^+, 50), 207(M^+-103, 100), IR (KBr): 1743 and 1739(C=O) cm^{-1}.

ACKNOWLEDGEMENTS

This paper is dedicated to Prof. Dr. Wolfgang Pfleiderer and Prof. Dr. Peter Boeger, Konstanz University, Germany, who were always giving me hearty encouragement and helpful suggestions throughout the cooperative works in Heterocyclic Chemistry and Biochemistry.

REFERENCES

1. Y. Miyamoto, *J. Heterocycl. Chem*., 2002, **39**, 157.
2. F. Troxler, H. P. Weber, A. Jaunin, and H. Loosli, *Helv. Chim. Acta*, 1974, **57**, 750.
3. R. Grigg and J. L. Jackson, *J. Chem. Soc.* (C), 1970, 552.
4. H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Am. Chem. Soc*., 1970, **92**, 4340.
5. C. W. Bird, *Tetrahedron*, 1992, **48**, 335.
6. H. Yamanaka, T. Hino, M. Nakagawa, and T. Sakamoto, New Heterocyclic Compounds (Shinpen Hetero-kan Kagoubutsu), p. 28, Kodan-sha Scientific (2004).
7. C. Yamazaki, K. Katayama, and K. Suzuki, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3085.
8. Z. Györogydeak, G. Szabo, and W. Holzer, *Monat. Chem*., 2004, **135**, 173.