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The Application of Unsymmetrical Vinylogous Iminium Salts and Related Synthons to the Preparation of Monosubstituted Triazolo[1,5-*a*]pyrimidines

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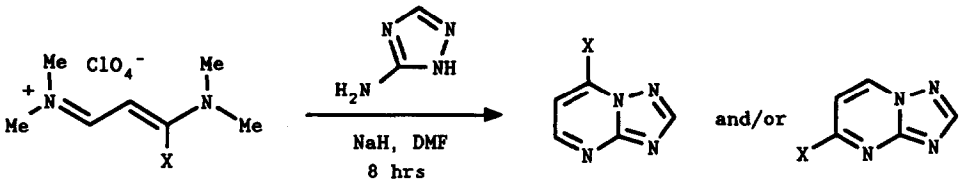
Abstract: The reaction of vinylogous iminium salts and related analogs with 3-amino-1,2,4-triazole to yield 7-substituted and 5-substituted triazolo[1,5-*a*]pyrimidines is described.

Since the discovery that many triazolopyrimidines have shown significant herbicidal activity,[1,2] there has been much activity in the synthesis of triazolopyrimidine derivatives and related compounds. The substitution pattern on the triazolopyrimidine greatly influences the degree of activity and the mode of action, so it is important to develop syntheses with regiochemical control. There is a very limited amount of literature on the synthesis of 7-substituted (**2**) and 5-substituted (**3**) triazolo[1,5-*a*]pyrimidines. Selby et al. have reported a synthesis resulting in a mixture of isomers by refluxing 1,3-dicarbonyl compounds and 3-amino-1,2,4-triazole in acetic acid.[2] Paudler et al. also obtained mixtures when treating triazolopyrimidine with phenyllithium.[3] Sirakawa was able to prepare the same triazolopyrimidines individually but through procedures involving several steps.[4] Consequently, none of these routes are appealing for a systematic approach to evaluating biological activity of triazolopyrimidines.

In a recent, previous paper, we have reported the synthesis of 6-substituted triazolo[1,5-*a*]pyrimidines from symmetrical vinamidinium

salts under basic conditions.[5] If unsymmetrical vinamidinium salts are used, it should be possible to obtain 7-substituted and 5-substituted triazolopyrimidines. The reactions of unsymmetrical vinamidinium salts with glycine derivatives to form pyrroles have been proposed to be under steric control.[6] If a similar mechanism is followed in the formation of triazolopyrimidines, a 7-substituted triazolopyrimidine should result (SCHEME 1). Such a reaction was found to be temperature dependent and the results are shown in TABLE 1. At lower temperatures only the 7-substituted isomer (**2**) was obtained in good yields. At higher temperatures both isomers were obtained in lower yields, but the 7-substituted isomer (**2**) was still the major product.

SCHEME 1



1 2 3

TABLE 1

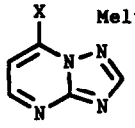
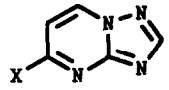
COMPOUND	X	TEMP(°C)	PROD[a]	% YIELD	TEMP(°C)	2:3 RATIO[a]	% YIELD
a	3,4-$(MeO)_2$Ph	100	2	83	reflux	>95:1	31
b	4-MeOPh	100	2	74	reflux	20:1	74
c	4-MePh	rt	2	85	100	4:1	45
d	Ph	100	2	79	reflux	5:1	66
e	4-BrPh	rt	2	44	100	2:1	33
f	4-ClPh	rt	2	93	100	4:1	76
g	3-NO_2Ph	rt	2	94	reflux	2:1	76
h	4-NO_2Ph	rt	2	86	100	5:1	31
i	4-FPh	rt	2	67	100	---[b]	--[b]

[a] products and ratios were determined by ^{1}H NMR.

[b] no starting material or desired products were observed by ^{1}H NMR.

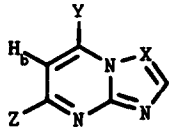
Since a minor isomer (**3f**) was isolated and completely characterized, the structure of each isomer could be determined by comparison of their melting points and proton NMR spectra with known samples. The melting points of the triazolopyrimidines that were prepared from the vinylogous iminium salts were consistent with the literature values shown in TABLE 2. The minor isomer (**3f**) has a higher melting point than the major isomer (**2f**). The proton-proton coupling constants shown in TABLE 3 are consistent between the parent systems, imidazolopyrimidine (**4**) and triazolopyrimidine

TABLE 2

X	Melting point (°C) 	
Ph, Lit. value[4]	141	186
Ph	146	---
4-ClPh	247	257

(5). The coupling constant of the known 5-substituted imidazolopyrimidine (6) is 6.9 Hz which is consistent with the minor isomer (3f) coupling constant of 7.2 Hz. The coupling constant of the major isomer (2f) is 4.6 Hz and is consistent with the 7-substituted imidazolopyrimidine (7) coupling constant of 4.3 Hz. The coupling constants of the substituted compounds were also consistent with the parent compounds. These comparisons enabled us to determine that the 7-substituted isomer (2) was the major isomer.

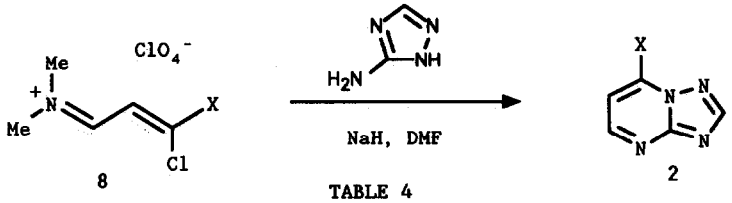
TABLE 3



COMPOUND	X	Y	Z	SOLVENT	J_{ab}	J_{bc}	J_{ac}
4[3]	CH	H_a	H_c	$CDCl_3$	6.9	4.1	2.0
5	N	H_a	H_c	$CDCl_3$	6.8	4.2	1.9
6[3]	CH	H_a	Ph	$CDCl_3$	6.9	---	---
7	CH	Ph	H_c	$CDCl_3$	---	4.3	---
2f	N	4-ClPh	H_c	DMSO-d_6	---	4.6	---
3f	N	H_a	4-ClPh	DMSO-d_6	7.2	---	---
2a	N	3,4-$(MeO)_2$Ph	H_c	DMSO-d_6	---	4.8	---
2b	N	4-MeOPh	H_c	DMSO-d_6	---	4.9	---
2c	N	4-MePh	H_c	DMSO-d_6	---	4.8	---
2d	N	Ph	H_c	DMSO-d_6	---	4.6	---
2e	N	4-BrPh	H_c	DMSO-d_6	---	4.7	---
2g	N	3-NO_2Ph	H_c	DMSO-d_6	---	4.7	---
2h	N	4-NO_2Ph	H_c	DMSO-d_6	---	4.6	---
2i	N	4-FPh	H_c	DMSO-d_6	---	4.7	---

Since we are able to make the 7-substituted triazolopyrimidine in one step from the unsymmetrical vinamidinium salt, we decided to expand our efforts to related systems. From previous studies involving the vinylogous iminium salts,[7] chloropropeniminium salts **(8)**, which are precursors to unsymmetrical vinamidinium salts **(1)**, may offer different regiochemical control and provide an opportunity to form the 5-substituted isomer. However, when the chloropropeniminium salts were reacted under similar conditions, the same regiochemistry was observed (SCHEME 2) as indicated in TABLE 4. No minor isomer **(3)** was observed by ^{1}H NMR even at higher temperatures.

SCHEME 2



8 2

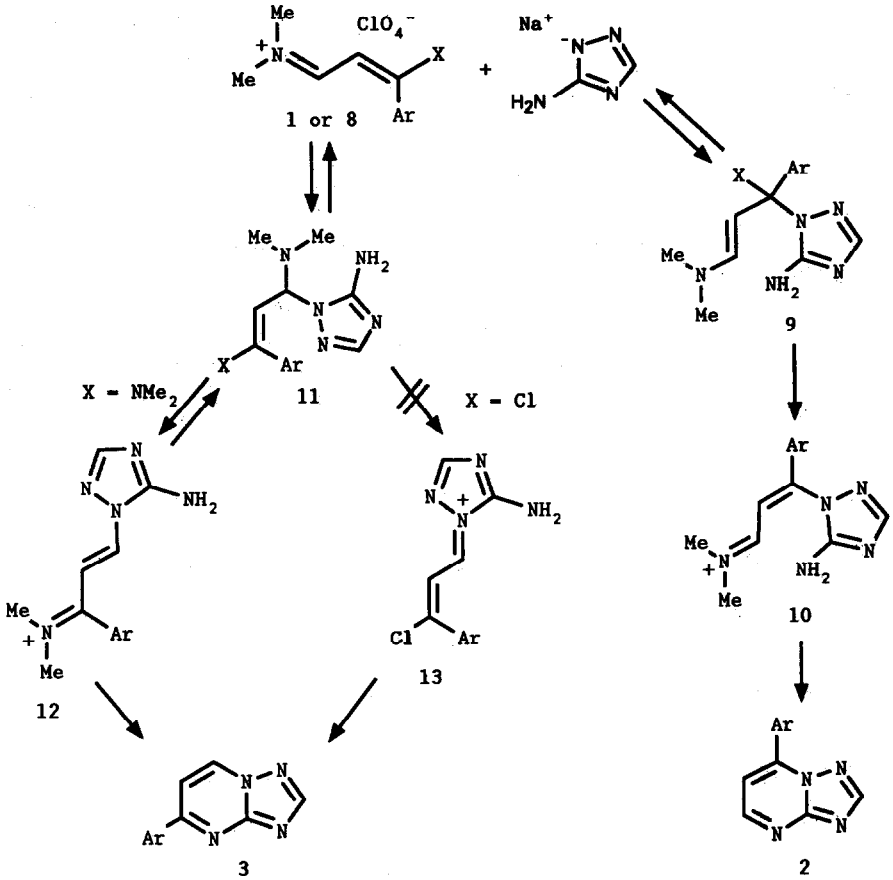
TABLE 4

Compound	X	TEMP(°C)	TIME(hr)	% YIELD
a	3,4-$(MeO)_2$Ph	100	8	52
b	4-MeOPh	100	8	93
c	4-MePh	100	8	73
d	Ph	rt, 1 hr and reflux, 1 hr		88
e	4-BrPh	rt	12	76
f	4-ClPh	rt	12	86
g	3-NO_2Ph	70	8	59
h	4-NO_2Ph	rt	8	---[a]
i	4-FPh	rt, 1 hr and reflux, 1 hr		100

[a] no starting materials or desired products were observed by ^{1}H NMR.

A proposed mechanism is shown in SCHEME 3. The anion of aminotriazole can attack the vinylogous iminium salts at two different electrophilic sites. For the chloropropeniminium salt **(8)**, previous work[7] has demonstrated that amine nucleophiles attack at the more electrophilic carbon, which is the carbon bearing the chlorine and aryl group, to give intermediate **(9)**. Irreversible loss of chloride ion would yield vinylogous iminium salt **(10)** which is shown in the favored configuration where the aryl group is trans to the iminium group. This geometry allows for fast cyclization to form the major isomer **(2)**. For the vinamidinium salt **(1)**, attack at the least sterically hindered site would be preferred forming intermediate **(11)**. Reversible loss of dimethylamide would yield vinylogous iminium salt **(12)** shown in its favored configuration where the

SCHEME 3



aminotriazole group is trans to the iminium group. This geometry does not allow for easy cyclization and the reverse reactions can occur. Attack of aminotriazole anion at the more sterically hindered position of vinamidinium salt (1) would lead to vinylogous iminium salt (10) which has a more favorable geometry for cyclization resulting in the major isomer (2). Lower temperatures allow for equilibration to occur resulting in the major isomer (2). The minor isomer (3) is formed at higher temperatures by cyclization of vinylogous iminium salt (12), but the major isomer is still favored. No minor isomer is formed in the chloropropeniminium salt reaction since intermediate (12) is not possible. Formation of the minor isomer would involve an unfavorable intermediate (13) which forfeits the aromaticity of the triazole ring.

Since the controlling factors in this process were interesting, we decided to take a broader approach to determine if the 5-substituted triazolopyrimidine (3) could be synthesized independently or as a major

product. We studied the reaction of a variety of three-carbon synthons that are closely related to the vinylogous iminium salts with aminotriazole under basic (sodium hydride, DMF reflux), neutral (DMF reflux), and acidic (acetic acid reflux) conditions (SCHEME 4). The

SCHEME 4

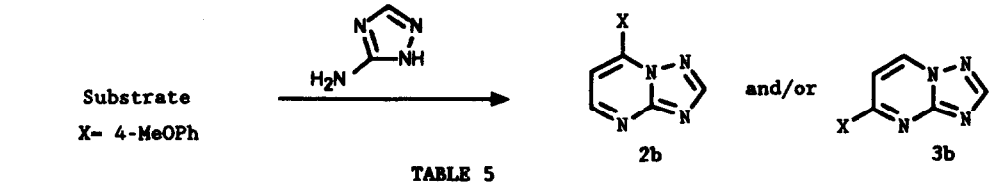
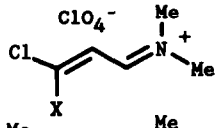
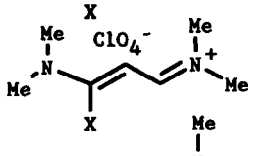
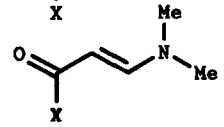
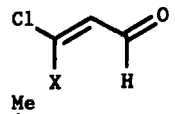
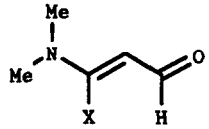


TABLE 5

SUBSTRATE	COMPOUND	CONDITIONS	PRODUCT(S)[a]	% YIELD
	8b	Basic	2b	93
		Neutral	NR[b]	--
		Acidic	2b	6
	1b	Basic	2b	74
		Neutral	2b	52
		Acidic	NR[b]	--
	14	Basic	2b	30
		Neutral	2b	64
		Acidic	2b	73
	15	Basic	2b	51
		Neutral	2b:3b (1:1)	54
		Acidic	2b	74
	16	Basic	2b	14
		Neutral	2b	17
		Acidic	2b:3b (2:1)	45

[a] products and ratios were determined by ^{1}H NMR.

[b] only starting materials were observed by ^{1}H NMR.

three-carbon synthons included a vinylogous amide (**14**), the chloropropeniminium (**8b**) and vinamidinium salt (**1b**), and their hydrolyzed products which are the β-chloroenal (**15**) and vinylogous formamide (**16**), respectively. The results of these reactions are summarized in TABLE 5.

In all of the examples studied, we were unable to obtain the 5-substituted triazolopyrimidine as the major isomer, and in most cases, only the 7-substituted triazolopyrimidine was obtained. Two reactions involving the aldehydes (**15**) and (**16**) gave the 5-substituted triazolopyrimidine (**3b**) in minor or equal amounts. It is interesting to note that the conditions which afforded a mixture of isomers with the aldehydes **15** and **16** gave no reaction with their respective vinylogous iminium salt

precursors.

In summary, we have synthesized a series of new 7-substituted triazolo[1,5-*a*]pyrimidines from either unsymmetrical vinamidinium salts or chloropropeniminium salts in very good yields. These reactions occur with significant regiochemical control and, in some cases, small amounts of the minor isomer can be obtained. The cleanest route to 7-substituted triazolopyrimidines with best yields uses the reaction of aminotriazole with unsymmetrical vinamidinium salts. To obtain the 5-substituted isomer, the reaction of aminotriazole with β-chloroenals is the best route. The overall process provides a clean and efficient method for obtaining the biologically important triazolo[1,5-*a*]pyrimidines.

EXPERIMENTAL

The following procedures are typical of the experimental conditions used for the preparation of 7-substituted triazolopyrimidines. The vinylogous iminium salts were prepared by standard methods.[8] All melting points and boiling points are uncorrected and all purified compounds gave a single spot upon TLC analysis on silica gel 7GF using an ethyl acetate/hexane mixture as eluent. Some of the reactions described require the use of a mixture of NaH and DMF. Various investigators have on occassion reported vigorous exothermic reactions under such conditions and appropriate caution and safety measures should be exercised.

7-(4-Methoxyphenyl)-1,2,4-triazolo-[1,5-*a*]pyrimidine (2b). A dry, 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer and placed under a nitrogen atmosphere. Into the flask was placed a 60% mineral oil dispersion of sodium hydride (0.15 g, 3.75 mmoles). The dispersion was washed twice with about 20 mL of dry hexane and the hexane was removed via cannula. To the flask was successively added 20 mL of dry DMF and 3-amino-1,2,4-triazole (0.19 g, 2.26 mmoles). After the mixture was allowed to react for 15 minutes, vinamidinium salt (**1b**) (0.5 g, 0.015 moles) was added. The resulting mixture was heated at 100 °C for 8 hours. The solvent was removed in vacuo and 30 mL of water was added. The resulting water-insoluble solid was washed with water, collected by vacuum filtration, and dried in vacuo leaving 0.25 g (74% yield) of the desired product. The product was recrystallized from an 80:20 THF:hexane mixture. The purified product exhibited the following properties: mp 197-198 °C; ^{1}H NMR (DMSO-d_6) δ 3.91 (s, 3H), 7.22 (d, J = 9.1 Hz, 2H), 7.64 (d, J = 4.9 Hz, 1H), 8.31 (d, J = 9.1 Hz, 2H), 8.75 (s, 1H) and 8.92 (d, J = 4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 57.6, 110.2, 116.4, 123.7, 133.2, 150.1, 156.3, 157.7 and 164.5; IR (KBr pellet) 1610, 1543, 1507, 1250 and 1030 cm^{-1}; HRMS for $C_{12}H_{10}N_4O$

calcd. 226.0855, found 226.0850. The subsequent compounds **(2a-2i)** were prepared in a manner identical to the preparation of compound **(2b)** with the exception that the appropriate vinamidinium salt was used as one of the starting materials.

7-(3,4-Dimethoxyphenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (2a): This compound was prepared in 83% yield and exhibited the following properties: mp 245-247 °C; ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 3.90 (s, 3H) 7.24 (d, J = 8.7 Hz, 1H), 7.69 (d, J = 4.8 Hz, 1H), 7.88 (broad s, 1H), 7.99 (d, J = 8.7 Hz, 1H), 8.76 (s, 1H) and 8.92 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 57.6, 110.6, 113.2, 114.6, 123.3, 125.3, 148.8, 150.2, 153.6, 156.5, 157.3 and 157.7; IR (KBr pellet) 3037, 2942, 2837, 1607, 1543, 1514, 1255, 1232 and 1038 cm^{-1}; HRMS for $C_{13}H_{12}N_4O_2$ calcd. 256.0960, found 256.0959.

7-(4-Methylphenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (2c): This compound was prepared in 85% yield and exhibited the following properties: mp 191-192 °C; ^{1}H NMR (DMSO-d_6) δ 2.45 (s, 3H), 7.47 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 4.8 Hz, 1H), 8.15 (d, J = 8.1 Hz, 2H), 8.75 (s, 1H) and 9.94 (d, J = 4.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 22.9, 111.0, 128.5, 131.1, 131.3, 143.8, 149.1, 156.7, 157.3 and 157.6; IR (KBr pellet) 3066, 2915, 1607, 1543 and 1507 cm^{-1}; HRMS for $C_{12}H_{10}N_4$ calcd. 210.0905, found 210.0901.

7-Phenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (2d): This compound was prepared in 79% yield and exhibited the following properties: mp 146 °C; ^{1}H NMR (DMSO-d_6) δ 7.63-7.69 (m, 4H), 8.19-8.23 (m, 2H), 8.75 (s, 1H) and 8.97 (d, J = 4.6 Hz, 1H); ^{13}C NMR δ 111.5, 130.5, 131.3, 133.5, 149.1, 156.9, 157.3 and 157.5; IR (KBr pellet) 3052, 1610, 1578, 1540 and 1494, cm^{-1}; HRMS for $C_{11}H_8N_4$ calcd. 196.0749, found 196.0749.

7-(4-Bromophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (2e): This compound was prepared in 44% yield and exhibited the following properties: mp 238-240 °C; ^{1}H NMR (DMSO-d_6) δ 7.68 (d, J = 4.7 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 8.18 (d, J = 8.7 Hz, 2H), 8.76 (s, 1H) and 8.98 (d, J = 4.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 110.9, 128.9, 130.4, 132.8, 134.3, 149.2, 156.4, 158.0 and 158.3; IR (KBr pellet) 1613, 1588, 1542, 1487 and 1086 cm^{-1}; HRMS for $C_{11}H_7N_4Br$ calcd. 273.9854, found 273.9856.

7-(4-Chlorophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (2f): This compound was prepared in 93% yield and exhibited the following properties: mp 247-248 °C; ^{1}H NMR (DMSO-d_6) δ 7.67 (d, J = 4.7 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 8.25 (d, J = 8.5, 2H), 8.75 (s, 1H) and 8.97 (d, J = 4.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 111.6, 130.2, 130.7, 133.2, 138.3, 146.9, 147.9, 156.9 and 157.3; IR (KBr pellet) 3062, 1615, 1593, 1543, 1490, 1093 cm^{-1}; HRMS for $C_{11}H_7N_4Cl$ calcd. 230.0359, found 230.0357.

7-(3-Nitrophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (2g): This compound was prepared in 94% yield and exhibited the following properties: mp

274-276 °C; ^{1}H NMR (DMSO-d_6) δ 7.82 (d, J = 4.6 Hz, 1H), 7.97 (t, J = 8.1 Hz, 1H), 8.53 (d, J = 7.1 Hz, 1H), 8.61 (d, J = 7.1 Hz, 1H), 8.82 (s, 1H), 9.04 (d, J = 4.6 Hz, 1H) and 9.13 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 81.0, 112.2, 126.3, 127.9, 132.2, 132.8, 137.7, 146.8, 149.5, 157.0 and 157.4 cm^{-1}; IR (KBr pellet) 3095, 3049,1607, 1543, 1514 and 1349 cm^{-1}; HRMS for $C_{11}H_7N_5O_2$ calcd. 241.0600, found 241.0605.

7-(4-Nitrophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (2h): This compound was prepared in 86% yield and exhibited the following properties: mp 255-256 °C; ^{1}H NMR (DMSO-d_6) δ 7.77 (d, J = 4.6 Hz, 1H), 8.49 (broad s, 4H), 8.80 (s, 1H) and 9.06 (d, J = 4.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 112.5, 125.5, 132.9, 137.4, 147.0, 150.7, 157.1 and 157.4; IR (KBr pellet) 3123, 3077, 1596, 1541, 1520, 1490 and 1347 cm^{-1}; HRMS for $C_{11}H_7N_5O_2$ calcd. 241.0600, found 241.0602.

7-(4-Fluorophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (2i): This compound was prepared in 67% yield and exhibited the following properties: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 7.52 (t, J = 8.8 Hz, 2H), 7.66 (d, J = 4.7 Hz, 1H), 8.32 (d of d, J = 8.8 Hz, J = 5.7 Hz, 2H), 8.76 (s, 1H) and 8.97 (d, J = 4.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 111.4, 117.7 (d, J = 20.0 Hz, 2C), 127.9 (d, J = 3.1 Hz, 1C), 134.1 (d, J = 9.2 Hz, 2C), 148.1, 156.8, 157.3, 157.5 and 165.7 (d, J = 250.7, 1C); IR (KBr pellet) 3049, 1607, 1549, 1514 and 1230 cm^{-1}; HRMS for $C_{11}H_7N_4F$ calcd. 214.0655, found 214.0654.

5-(4-Chlorophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (3f): This isomer was separated from the major isomer **(2f)** by radial chromatography through a gradient elution using hexane and ethyl acetate as the eluent. The purified product exhibited the following properties: mp 257-258 °C; ^{1}H NMR (DMSO-d_6) δ 7.70 (d, J = 8.7 Hz, 2H), 8.04 (d, J = 7.2 Hz, 1H), 8.36 (d, J = 8.6 Hz, 2H), 8.73 (s, 1H) and 9.53 (d, J = 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 109.6, 131.0, 131.3, 136.5, 138.2, 139.6, 156.5, 158.4 and 161.5; IR (KBr pellet) 3098, 3081, 1630, 1596, 1537, 1494, 1418 and 1097 cm^{-1}; HRMS for $C_{11}H_7N_4Cl$ calcd. 230.0359, found 230.0364.

7-Phenylimidazo[1,2-*a*]pyrimidine (7): A dry 100-mL, three-neck round-bottom flask was equipped with a reflux condenser and magnetic stirrer and placed under nitrogen atmosphere. Into the flask was placed a 60% mineral oil dispersion of sodium hydride (0.17 g, 4.16 mmoles). The dispersion was washed twice with 20 mL of dry hexane and the hexane was removed via cannula. To the flask was successively added 20 mL of dry DMF and 2-aminoimidazole sulfate (0.33 g, 2.48 mmoles) and the mixture was allowed to react for 15 minutes. The vinamidinium salt **(1d)** (0.5 g, 1.65 mmoles) was added and the mixture was heated at 100 °C for 8 hours. The solvent was removed in vacuo. Water was added to the residue and it was extracted three times with chloroform. The combined chloroform extracts

were dried and concentrated in vacuo leaving 0.25 g (78 % yield) of a brown oil. The product was purified by radial chromatography using a gradient elution of ethyl acetate and hexane. The purified product exhibited the following properties: mp 174-176 °C; ^{1}H NMR ($CDCl_3$) δ 6.84 (d, J = 4.3 Hz, 1H), 7.59-7.70 (m, 6H), 7.83 (d, J = 1.4 Hz, 1H) and 8.62 (d, J = 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 110.2, 111.1, 129.9, 131.5, 133.1, 134.1, 137.3, 148.2, 151.6 and 152.0; IR (KBr pellet) 3043, 1612, 1532 and 1492 cm $^{-1}$; HRMS for $C_{12}H_9N_3$ calcd. 195.0796, found 195.0793.

Reactions with Chloropropeniminium Salts: A dry, 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer, and placed under a nitrogen atmosphere. Into the flask was placed a 60% mineral oil dispersion of sodium hydride (0.59 g, 14.8 mmoles). The dispersion was washed twice with dry hexane and the hexane was removed via cannula. To the flask was successively added 25 mL of dry DMF and 3-amino-1,2,4-triazole (0.74 g, 8.80 mmoles). After the mixture was allowed to react for 15 minutes, chloropropeniminium salt (**8**) (5.90 mmoles) was added. The resulting mixture was heated at 100 °C for 8 hours. The solvent was removed in vacuo and partitioned three times between water and chloroform. The combined chloroform extracts were dried and concentrated in vacuo yielding the triazolopyrimidine (**2**). All of the physical properties matched those of the corresponding products prepared from the vinamidinium salts (**1**).

1-(4-Methoxyphenyl)-3-(dimethylamino)-2-propenone (14): A dry, 150-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer. Into the flask was placed 20 mL of DMF, 5.0 g (33.3 mmoles) of 4'-methoxyacetophenone and 15.87 g (133.0 mmoles) of the diethyl acetal of DMF. The resulting solution was heated at reflux for eight hours. The DMF and the unreacted DMF acetal were removed in vacuo leaving 5.0 g (74% yield) of a yellow solid when cooled to room temperature. This material had the following properties: mp 95-96 °C; ^{1}H NMR ($CDCl_3$) δ 3.00 (broad s, 6H), 3.80 (s, 3H), 5.67 (d, J = 12.3 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 12.3 Hz, 1H) and 7.87 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 39.3, 46.5, 57.3, 93.6, 115.3, 131.4, 135.1, 155.8, 163.7 and 189.3; IR (KBr pellet) 3006, 2911, 2837, 1636 and 1363 cm^{-1}; HRMS for $C_{12}H_{15}NO_2$ calcd. 205.1103, found 205.1101.

3-Chloro-3-(4-methoxyphenyl)-2-propenal (15): A 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer. Into the flask was placed 2.0 g (5.4 mmoles) of chloropropeniminium salt (**8b**) and 30 mL of 50:50 water:THF. The mixture was heated at 65-70 °C for 4 hours. After the THF was removed in vacuo, the solution was extracted three times with chloroform. The combined chloroform

extracts were dried and concentrated in vacuo leaving 0.8 g (76% yield) of a brown solid which had the following properties: mp 58-60 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 6.62 (d, J = 7.0 Hz, 1H), 6.95 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 9.0 Hz, 2H) and 10.18 (d, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 57.6, 116.3, 124.5, 129.6, 131.0, 154.2, 164.7 and 193.7; IR (KBr pellet) 3423, 1664, 1398, 1273 and 1022 cm^{-1}; HRMS for $C_{10}H_9O_2Cl$ calcd. 196.0291, found 196.0285.

3-(4-Methoxyphenyl)-3-(dimethylamino)-2-propenal (16): A 150-mL round-bottom flask was equipped with a reflux condenser and magnetic stirrer. Into the flask was placed 4.0 g (10.6 mmoles) of vinamidinium salt (**1b**), 6.72 g (63.4 mmoles) of sodium carbonate and 70 mL of 50:50 water:THF. The mixture was heated at reflux for 24 hours. After the THF was removed in vacuo, the water phase was extracted three times with chloroform. The combined chloroform extracts were dried and concentrated in vacuo and distilled at 160-172 °C (25-28 torr). The distillate was then purified by radial chromatography using a gradient elution of hexane and ethyl acetate. A 30% yield of a light brown oil was obtained which had the following properties: bp 162 °C at 25 torr; ^{1}H NMR ($CDCl_3$) δ 2.76 (broad s, 3H), 2.99 (broad s, 3H), 3.82 (s, 3H), 5.35 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H) and 8.64 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 57.4, 79.3, 105.6, 115.8, 128.0, 132.7, 162.4, 170.6 and 193.1; IR ($CDCl_3$) 3417 (broad), 2937, 2838, 1609, 1386, 1251 and 1027 cm^{-1}; HRMS for $C_{12}H_{15}NO_2$ calcd. 205.1103, found 205.1098.

Reactions Performed under Basic Conditions: A dry, 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer, and placed under a nitrogen atmosphere. Into the flask was placed a 60% mineral oil dispersion of sodium hydride (0.15 g, 3.83 mmoles). The dispersion was washed twice with dry hexane and the hexane was removed via cannula. To the flask was added 20 mL of dry DMF and 3-amino-1,2,4-triazole (0.19 g, 2.30 mmoles). After the mixture was allowed to react for 15 minutes, β-chloroenal (**15**) (0.3 g, 1.53 mmoles) was added. The resulting mixture was heated at reflux for 0.5 hours. The solvent was removed in vacuo and 30 mL of water was added. The resulting water-insoluble solid was collected by vacuum filtration and dried in vacuo leaving 0.18 g (51% yield) of triazolopyrimidine (**2b**). The product mixture was analyzed by TLC and ^{1}H NMR and compared to authentic samples.

Reactions Performed under Neutral Conditions: A dry, 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer, and placed under a nitrogen atmosphere. To the flask was successively added 20 mL of dry DMF, 3-amino-1,2,4-triazole (0.19 g, 2.30 mmoles) and β-chloroenal (**15**) (0.3 g, 1.53 mmoles). The resulting

mixture was heated at reflux for 3.5 hours. The solvent was removed in vacuo and 30 mL of water was added. The resulting water-insoluble solid was collected by vacuum filtration and dried in vacuo leaving 0.19 g (54% yield) of a mixture of triazolopyrimidines **(2b)** and **(3b)**. The product was analyzed by TLC and ^{1}H NMR and compared to authentic samples.

Reactions Performed under Acidic Conditions: A dry, 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer. To the flask was added 20 mL of glacial acetic acid, 3-amino-1,2,4-triazole (0.13 g, 1.53 mmoles) and β-chloroenal **(15)** (0.2 g, 1.02 mmoles). The resulting mixture was heated at reflux for 19 hours and cooled. The reaction mixture was poured into 100 mL of water. The water-insoluble solid was collected by vacuum filtration and dried in vacuo leaving 0.19 g (74% yield) of triazolopyrimidine **(2b)**. The product was analyzed by TLC and ^{1}H NMR and compared to authentic samples.

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REFERENCES

1. W. Kleschick, R. Ehr, B. Gerwick, W. Monte, N. Pearson, M. Costales, and R. Meikle, *US Patent* #4,740,233, **1988**.
2. T. Selby, T. Andrea, L. Denes, B. Finkelstein, T. Fuesler, and B. Smith, *'Synthesis and Chemistry of Agrochemicals III,'* D. Baker, J. Fenyes, and J. Steffens, ed., American Chemical Society, Washington, DC. **1992**, pp. 91-102.
3. W. Paudler, C. Chao, and L. Helmick, *J. Heterocyclic Chem.*, **1972**, 1157.
4. K. Sirakawa, *J. Pharm. Soc. Japan*, 1960, **86**, 956.
5. S. Petrich, Z. Qian, L. Santiago, J. Gupton, and J. Sikorski, *Heterocycles*, manuscript submitted.
6. Lana L. Smith, master's thesis, **1993**, University of Central Florida.
7. J. Gupton, D. Krolikowski, R. Yu, P. Vu, J. Sikorski, M. Dahl, and C. Jones, *J. Org. Chem.*, 1992, **57**, 5480.
8. J. Liebscher and H. Hartmann, *Synthesis*, **1979**, 241.

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