THE APPLICATION OF SYMMETRICAL VINAMIDINIUM SALTS TO THE PREPARATION OF MONOSUBSTITUTED TRIAZOLO[1,5-*a*]-PYRIMIDINES[1]

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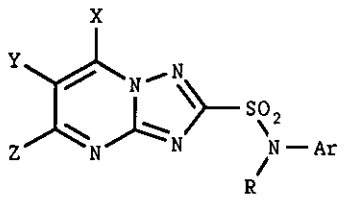
Abstract- The reaction of 2-substituted vinamidinium salts with 3-amino-1,2,4-triazole under basic conditions to yield 6-substituted triazolo[1,5-*a*]-pyrimidines is described.

The synthesis of triazolopyrimidine derivatives and related compounds has been actively pursued in recent years due in part to the discovery that triazolopyrimidines **(1)**[2] and **(2)**[3] have shown significant herbicidal activity. The degree of activity and the mode of action is strongly influenced by the substituents on the triazolopyrimidine and,



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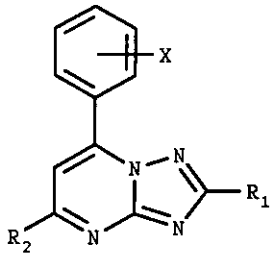

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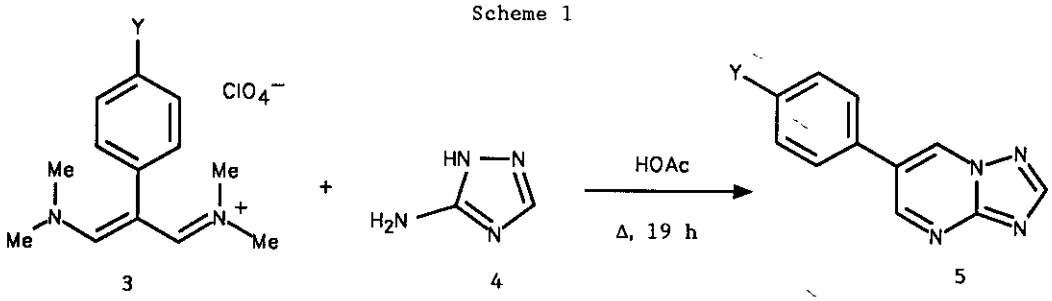
consequently, the efficient preparation of uniquely functionalized analogs becomes important. Our research group has been actively involved in using vinamidinium and chloropropeniminium salts as three carbon synthons for making heterocyclic compounds.[4] Interestingly, the patent literature does contain a reference for synthesizing triazolopyrimidines from vinamidinium salts under acidic conditions.[2] We have attempted several reactions under these reported conditions for the preparation of triazolopyrimidines but were unable to obtain consistent results. In particular, electron donating groups drastically reduce the formation of triazolopyrimidines (Scheme 1).

Scheme 1

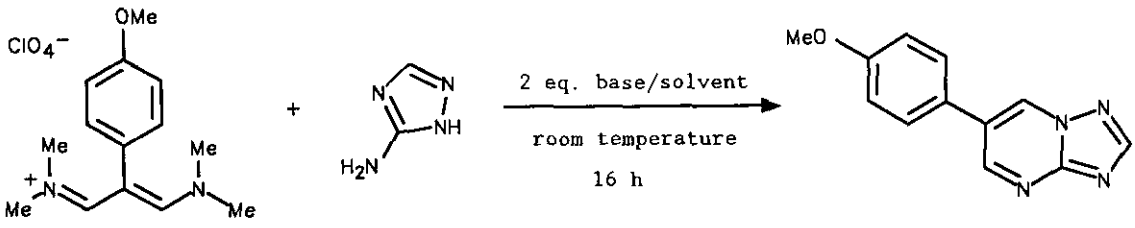


3 4 5

Compound	Y	% Yield
a	MeO	19
c	Me	No reaction
f	NO_2	69

We, therefore, decided to evaluate other conditions that might give optimized and consistent results across a range of substituents. We have been successful in the past with a variety of cyclization reactions involving vinamidinium salts under basic conditions.[5] Subsequently, a series of experiments were performed to determine the best base/solvent system to use for the cyclization of vinamidinium salt **(3a)** with 3-amino-1,2,4-triazole **(4)**. The base/solvent combinations and results are shown in Table 1. The best combination was sodium hydride and

Scheme 2



3a 4 5a

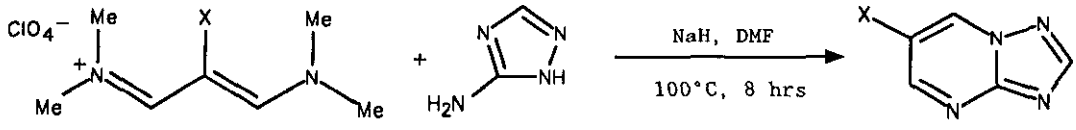
Table 1

Base	Solvent	Yield
Na_2CO_3	EtOH	No reaction
Na_2CO_3	MeCN	No reaction
Na_2CO_3	DMSO	9%
Na_2CO_3	DMF	13%
NaOEt	EtOH	No reaction
NaH	DMF	47%

dimethylformamide for our initial screening of conditions. These conditions were further optimized by using the Orthogonal Latin Square Design[6] which is an experimental design based upon statistical theory and

involves varying the stoichiometry, reaction time and reaction temperature. The value of the method is to provide significant information with a limited number of experiments. The optimized conditions were a 1:1.5 stoichiometry of vinamidinium salt **(3)**: 3-amino-1,2,4-triazole **(4)** with 2.5 equivalents of sodium hydride at 100 °C for 8 hours. The results using these optimized conditions are shown in Table 2. Very good isolated yields were obtained across a variety of

Scheme 3



3 4 5

Table 2

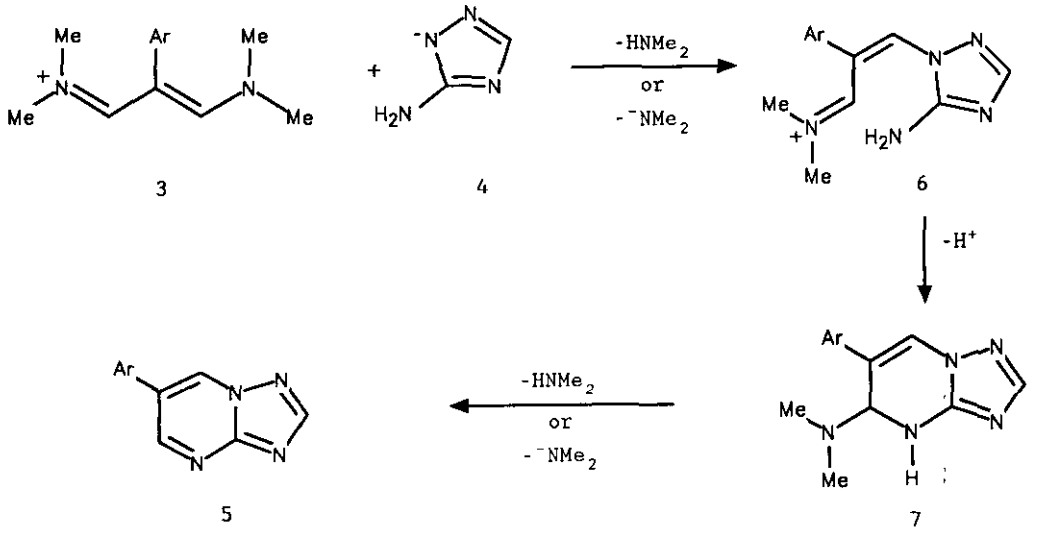
Compound	X	% Yield
a	4-MeOPh	76
b	3,4-$(MeO)_2$Ph	70
c	4-MePh	84
d	4-BrPh	79
e	4-ClPh	80
f	4-NO_2Ph	84
g	Ph	71
h	1-Naphthyl	85
i	1-Benzotriazolyl	69
j	$PhSO_2$	26

aryl substituents. We were also successful in synthesizing novel

triazolopyrimidines **(5i)** and **(5j)** which contain a benzotriazolyl and phenylsulfonyl moiety, respectively. These groups have already been shown to be pharmacophores[7] and are also useful synthetic auxillaries for further manipulation. The benzotriazolyl group is easily replaced by other groups such as Grignard reagents and may be a directing group for heteroatom directed metallation reactions.[8] The phenylsulfonyl group has been called a "chemical chameleon" by Trost since a diverse group of reactions are possible involving this moiety.[9]

A possible mechanism for the reaction is shown in Scheme 4. Under basic

Scheme 4



conditions the aminotriazole exists as the anion **(4)** and attacks the electophilic carbon of the vinamidinium salt **(3)**. Elimination of dimethylamine or dimethylamide results in the formation of amine exchanged product **(6)**. With the 2-substituted vinamidinium salts, the

molecule is symmetrical so the two electrophilic sites are identical. There are two other sites on 3-amino-1,2,4-triazole **(4)** where nucleophilic attack would also form amine exchange products. However, alkylation reactions performed under basic conditions have shown substitution occurs mostly at the "hydrazine-like" nitrogens of the aminotriazole.[10] The ring juncture is determined in this first step and the ring juncture shown has been proposed as the thermodynamic product in similar fused-ring systems.[11] Cyclization of the vinylogous iminium salt **(6)** followed by loss of another equivalent of dimethylamine or dimethylamide from intermediate **(7)** should afford the observed triazolopyrimidine **(5)**. The presence of a base presumably facilitates the nucleophilic attack of aminotriazole **(4)** and cyclization of vinylogous iminium salt **(6)**. It is not obvious whether dimethylamine or dimethylamide is eliminated.

Since Kleschick *et al.*[12] have reported the X-ray structure for similar triazolo[1,5-*a*]pyrimidines, the structure proof for triazolopyrimidines **(5)** prepared under our basic conditions was conducted by comparing ^{1}H nmr, tlc and mp with those of the same compound obtained using Kleschick's acetic acid conditions. In addition, high resolution mass spectral analysis was obtained for all products.

In summary, we have synthesized a wide variety of 6-substituted triazolo[1,5-*a*]pyrimidines from 2-substituted vinamidinium salts in good yield. The series includes novel triazolopyrimidines which contain a benzotriazolyl and phenylsulfonyl group as substituents. The sodium hydride/dimethylformamide system gave consistent yields and should

provide a convenient route to novel monosubstituted triazolo[1,5-*a*]-pyrimidines.

EXPERIMENTAL

The following procedures are typical of the experimental conditions used for the preparation of 6-substituted triazolopyrimidines. The vinamidinium salts were synthesized in the same manner as described by Gupton *et al.*[13] All melting points and boiling points are uncorrected and all purified compounds gave a single spot by tlc analysis on silica gel 7GF with ethyl acetate/hexane mixture as eluent.

6-(4-Methoxyphenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (5a): 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 mmol). 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 mmol). After the mixture was allowed to react for 15 min, vinamidinium salt **(3a)** (0.5 g, 0.015 mol) was added. The resulting mixture was heated at 100 °C for 8 h. 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 under vacuum leaving 0.26 g (76% yield) of the product. The solid was recrystallized from ethanol/water. The purified product exhibited the following properties: mp 171-173 °C; ^{1}H nmr ($CDCl_3$) δ 3.89 (s, 3H), 7.08 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 8.53 (s, 1H), 8.94 (d, J = 2.5 Hz, 1H) and 9.07 (d, J = 2.5 Hz,

1H); ^{13}C nmr ($CDCl_3$) δ 57.5, 117.2, 127.0, 127.1, 130.4, 133.9, 156.3, 156.8, 158.4, 162.6; ir (KBr pellet) 3072, 2990, 2835, 1611, 1500, 1249 and 1024; Hrms for $C_{12}H_{10}N_4O$ calcd 226.0855, found 226.0860.

6-(3,4-Dimethoxyphenyl)-1,2,4-triazolo[1,5-a]pyrimidine (5b): This compound was prepared in 70% yield in a manner identical to the preparation of compound **(5a)** with the exception that vinamidinium salt **(3b)** was used as one of the starting materials. The purified product of this reaction exhibited the following properties: mp 177-180 °C; ^1H nmr ($CDCl_3$) δ 3.96 (s, 3H), 3.97 (s, 3H), 7.03 (m, 2H), 7.16 (d, J = 6.1 Hz, 1H), 8.53 (s, 1H), 9.01 (d, J = 2.5 Hz, 1H) and 9.08 (d, J = 2.5 Hz, 1H); ^{13}C nmr δ ($CDCl_3$) 58.1, 58.2, 112.1, 114.0, 121.9, 127.28, 127.34, 134.1, 151.9, 152.1, 156.3, 156.9 and 158.5; ir (KBr pellet) 3064, 2966, 2935, 2838, 1619, 1503, 1263, 1239, 1026 cm^{-1}; Hrms for $C_{13}H_{12}N_4O_2$ calcd 256.0960, found 256.0966.

6-(4-Methylphenyl)-1,2,4-triazolo[1,5-a]pyrimidine (5c): This compound was prepared in 84% yield in a manner identical to the preparation of compound **(5a)** with the exception that vinamidinium salt **(3c)** was used as one of the starting materials. The purified product of this reaction exhibited the following properties: mp 160-163 °C; ^1H nmr ($CDCl_3$) δ 2.44 (s, 3H), 7.36 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 8.53 (s, 1H), 8.97 (d, J = 2.3 Hz, 1H) and 9.08 (d, J = 2.3 Hz, 1H); ^{13}C nmr δ ($CDCl_3$) 23.2, 127.3, 129.0, 131.8, 132.4, 134.3, 141.5, 156.9 and 158.5; ir (KBr pellet) 3070, 1624 and 1498 cm^{-1}; Hrms for $C_{12}H_{10}N_4$ calcd 210.0905, found 210.0915.

6-(4-Bromophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (5d): This compound was prepared in 79% yield in a manner identical to the preparation of compound **(5a)** with the exception that vinamidinium salt **(3d)** was used as one of the starting materials. The purified product of this reaction exhibited the following properties: mp 199-203 °C; ^{1}H nmr ($CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 8.56 (s, 1H), 9.00 (d, J = 2.4 Hz, 1H) and 9.06 (d, J = 2.4 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 125.9, 126.2, 130.7, 133.7, 134.6, 135.0, 156.4 and 158.8; ir (KBr pellet) 3047, 1592, 1490 and 1077 cm^{-1}; Hrms for $C_{11}H_7N_4Br$ calcd 273.9854, found 273.9853.

6-(4-Chlorophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (5e): This compound was prepared in 80% yield in a manner identical to the preparation of compound **(5a)** with the exception that vinamidinium salt **(3e)** was used as one of the starting materials. The purified product of this reaction exhibited the following properties: mp 202-205 °C; ^{1}H nmr ($CDCl_3$) δ 7.55 (br s, 4H), 8.56 (s, 1H), 9.00 (d, J = 2.4 Hz, 1H) and 9.06 (d, J = 2.4 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 126.2, 130.5, 132.0, 133.3, 134.6, 137.8, 156.5 and 158.8; ir (KBr pellet) 3045, 1599, 1491 and 1094 cm^{-1}; Hrms for $C_{11}H_7N_4Cl$ calcd 230.0359, found 230.0359.

6-(4-Nitrophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (5f): This compound was prepared in 84% yield in a manner identical to the preparation of compound **(5a)** with the exception that vinamidinium salt **(3f)** was used as one of the starting materials. The purified product of this reaction exhibited the following properties: mp 240-243 °C; ^{1}H nmr (DMSO-d_6) δ 8.21 (d, J = 8.6 Hz, 2H), 8.40 (d, J = 8.6 Hz, 2H), 8.80 (s, 1H), 9.39 (d, J = 1.9 Hz, 1H) and 10.00 (d, J = 1.9 Hz, 1H); ^{13}C nmr (DMSO-d_6) δ

123.7, 126.0, 130.3, 137.3, 141.3, 149.2, 156.6 and 158.6; ir (KBr pellet) 3044, 1517 and 1351 cm^{-1}; Hrms for $C_{11}H_7N_5O_2$ calcd 241.0600, found 241.0602.

6-Phenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (5g): This compound was prepared in 71% yield in a manner identical to the preparation of compound **(5a)** with the exception that vinamidinium salt **(3g)** was used as one of the starting materials. The purified product of this reaction exhibited the following properties: mp 158-161 °C; ^1H nmr ($CDCl_3$) δ 7.53-7.59 (m, 5H), 8.55 (s, 1H), 9.01 (d, J = 2.5 Hz, 1H) and 9.10 (d, J = 2.5 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 127.3, 129.2, 131.3, 131.7, 134.6, 134.8, 156.9 and 158.6; ir (KBr pellet) 3049, 1624 and 1496 cm^{-1}; Hrms for $C_{11}H_8N_4$ calcd 196.0749, found 196.0757.

6-(1-Naphthyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (5h): This compound was prepared in 85% yield in a manner identical to the preparation of compound **(5a)** with the exception that vinamidinium salt **(3h)** was used as one of the starting materials. The product was purified by bulb-to-bulb distillation and exhibited the following properties: bp 164 °C at 0.12 torr; ^1H nmr ($CDCl_3$) δ 7.49-7.66 (m, 4H), 7.75-7.79 (m, 1H), 7.97-8.04 (m, 2H), 8.61 (s, 1H), 8.98 (d, J = 2.4 Hz, 1H) and 9.01 (d, J = 2.4 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 126.3, 126.4, 127.5, 128.7, 129.5, 130.4, 130.9, 132.0, 132.5, 133.4, 135.9, 136.9, 156.6, 158.7 and 158.9; ir ($CHCl_3$) 3060, 1624, and 1498 cm^{-1}; Hrms for $C_{15}H_{10}N_4$ calcd 246.0905, found 246.0903.

6-(1-Benzotriazolyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (5i): This compound

was prepared in 69% yield in a manner identical to the preparation of compound **(5a)** with the exception that vinamidinium salt **(3i)** was used as one of the starting materials. The purified product of this reaction exhibited the following properties: mp 218-220 °C; ^{1}H nmr (DMSO-d_6) δ 7.59 (t, J = 7.3 Hz, 1H), 7.74 (t, J = 7.3 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.91 (s, 1H), 9.42 (d, J = 2.5 Hz, 1H) and 10.26 (d, J = 2.5 Hz, 1H); ^{13}C nmr (DMSO-d_6) δ 112.9, 121.4, 124.5, 126.9, 130.8, 135.0, 135.4, 147.1, 153.9, 156.0 and 159.2; ir (KBr pellet) 3080, 1173, and 1070 cm^{-1}; Hrms for $C_{11}H_7N_7$ calcd 237.0763, found 237.0773.

6-(Phenylsulfonyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (5j): This compound was prepared in 26% yield in a manner identical to the preparation of compound **(5a)** with the exception that vinamidinium salt **(3j)** was used as one of the starting materials. The purified product of this reaction exhibited the following properties: mp 239-242 °C; ^{1}H nmr ($CDCl_3$) δ 7.57-7.74 (m, 3H) 8.04 (d, J = 8.4 Hz, 2H), 8.67 (s, 1H), 9.15 (d, J = 2.4 Hz, 1H) and 9.49 (d, J = 2.4 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 129.3, 129.9, 132.1, 136.8 139.3, 141.7, 154.6 and 160.9; ir (KBr pellet) 3075, 1326 and 1155 cm^{-1}; Hrms for $C_{11}H_8N_4O_2S$ calcd 260.0368, found 260.0364.

Reaction under acidic conditions: A solution of 0.53 g (6.32 mmol) of 3-amino-1,2,4-triazole and 2.10 g (6.32 mmol) of vinamidinium salt **(3a)** in 20 ml of glacial acetic acid was heated at reflux for 19 h. After cooling to room temperature, the solution was poured into 100 ml of water. The solid which separated was collected by vacuum filtration, washed with water and dried *in vacuo* leaving 0.27 g (19% crude yield) of

the desired product. The ^1H nmr and tlc were identical to compound **(5a)** upon comparison.

Base/solvent system study: Into a dry 100-ml, three-neck, round-bottom flask was placed a 60% mineral oil dispersion of sodium hydride (0.12 g, 3.0 mmol). The dispersion was washed twice with about 15 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 (0.14 g, 1.654 mmol). After the mixture was allowed to react for 15 min, the vinamidinium salt **(3a)** (0.5 g, 1.5 mmol) was added. The reaction was carried out at room temperature for 16 h. 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 0.16 g (47% yield) of the product. The same procedure and conditions as above were used for the reactions in the other base/solvent systems except for the following cases. For Na_2CO_3 in EtOH, MeCN, DMSO or DMF, a simple mixing was conducted. For NaOEt in EtOH, NaH was used to react with EtOH (in excess) to produce NaOEt.

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