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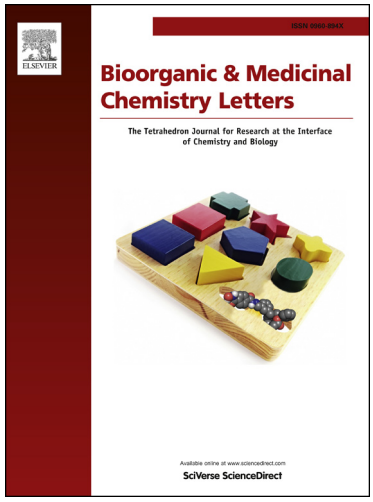

A one pot, two-step synthesis of 5-arylpyrrolo[2,3-*d*]pyrimidines and screening of their preliminary antibacterial properties

Lakhinath Saikia, P. Roudragouda, Ashim J. Thakur

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Graphical Abstract

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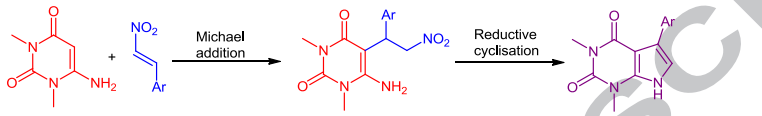

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A one pot, two-step synthesis of 5-arylpyrrolo[2,3-*d*]pyrimidines and screening of their preliminary antibacterial properties

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ABSTRACT

A one pot two step methodology for the synthesis of ten derivatives of 5-arylpyrrolo[2,3-*d*]pyrimidine has been reported. The methodology exploits the strong reducing nature of alkaline $Na_2S_2O_4$ solution coupled with favorability of Michael type addition reaction in alkaline medium. The methodology demands attraction as it is non-catalytic, quite general for wide range of nitrostyrenes and possesses comprehensive advantages over most of the earlier methods in terms of reaction time as well as yield. The methodology enjoys additional advantage of utilizing cheaper and easily available chemicals as reagent for the purpose.Some of the synthesized compounds are found to possess remarkable activity againstsome of the tested bacterial strains.

Among various fused heterocycles, pyrrolo[2,3-*d*]pyrimidines has been considered as one of the most important classes of organic compounds. Various compounds of this family have been designed, synthesized and screened towards various biological activities. A plentiful of pyrrolo[2,3-*d*]pyrimidines have been established to possess diverse biological activities like antifolate,[1] antitumour,[2] antibacterial,[3] antiviral,[4] receptor tyrosine kinase (RTK) inhibitor,[5] firefly luciferase inhibitor,[6] microtubule inhibitor,[7] affinity against α_1-adrenosine receptor (α_1-AR)[8] etc. Alimta (**1**, Fig. 1), a 5-substituted pyrrolo[2,3-*d*]pyrimidine has been established as a unique antifolate with remarkable activity against a broad spectrum of solid tumors.[9] The scaffold draws attention from the material chemists too due to its redox ability and interesting photophysical properties.[10] A plethora of reports have been found reporting the synthesis and biological evaluation of diversely substituted pyrrolo[2,3-*d*]pyrimidines.[11]However, only a few reports have been found for the synthesis of 5-arylpyrrolo[2,3-*d*]pyrimidine and to the best of our knowledge not a single report has been found to evaluate the biological significances of the synthesized compounds. Taylor *et al.* first reported the synthesis of eight derivatives of 5-arylpyrrolo[2,3-*d*]pyrimidine in a four-step process in modest yields[12] and another couples of reports have been published in subsequent days.[13]Herein, we report the synthesis of ten derivatives of 5-arylpyrrolo[2,3-*d*]pyrimidines in a one pot, two-step methodology using readily available and cheaper laboratory chemicals. A gentle attempt to carry out preliminary antibacterial studyof the synthesized compounds has been made.

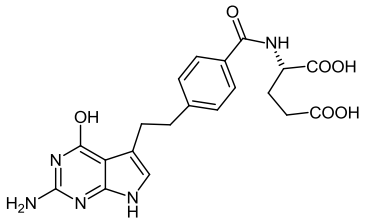
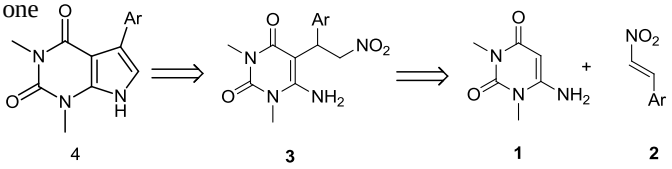


Figure 1. Structure of Alimta, an antifolate

Following the retrosynthetic analysis (Scheme 1) we sought to design an efficient, one pot synthetic methodology for 5-arylpyrrolo[2,3-*d*]pyrimidines (**4**) from aminopyrimidine(**1**) andnitrostyrenes (**2**).We targeted to carry out the synthesis in a one



Scheme 1. Retrosynthetic analysis of 5-arylpyrrolo[2,3-*d*]pyrimidine (**4**)

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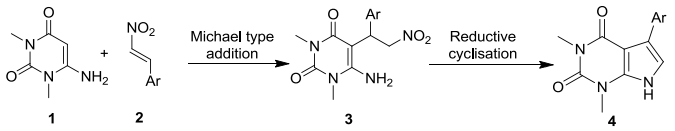
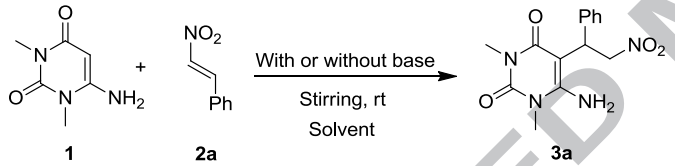
pot two-step process by exploiting two well known facts: (i) the favorability of Michael addition reaction in alkaline medium and (ii) the strong reducing capability of alkaline $Na_2S_2O_4$ solution. These two facts led us to the idea that there could be a useful synthetic route for pyrrolo[2,3-*d*]pyrimidine starting from aminopyrimidine (**1**) and nitrostyrene (**2**) by carrying out the Michael type addition (first step) in alkaline medium followed by reductive cyclisation of the Michael type adduct (second step) using alkaline $Na_2S_2O_4$ solution (Scheme 2). The complete process was expected to be carried out in a single pot, if both the steps would become successful in a common solvent.



Scheme 2. Proposed route for pyrrolo[2,3-*d*]pyrimidine

To start with, 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) was treated with (*E*)-(2-nitrovinyl)benzene (**2a**) in equimolar ratio in water at room temperature (Scheme 3). The starting materials were observed to be consumed completely within 6 hours resulting a single product which was later on confirmed as the Michael type adduct (**3a**) by single crystal X-ray analysis (Fig. 2).[14] The same reaction was then tested in presence of 1 equivalent of aqueous NaOHsolution and to our delight, it worked sufficiently well to reduce the time required for complete consumption of the substrates from 6 hrs to 2 hrs. Other



Scheme 3. Michael type addition between**1** &**2a**

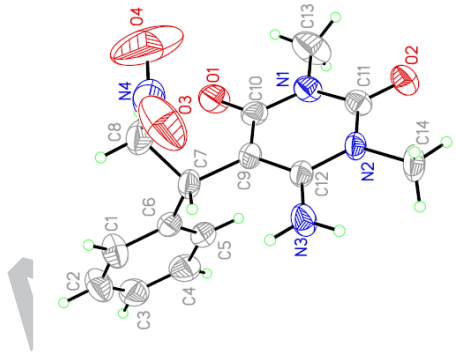


Figure 2. ORTEP diagram of **3a**

solvent-base combinations were also examined under identical conditions and the results are summarized in a bar diagram (Fig. 3). Fig. 3 clearly signifies the suitability of polar protic solvents over polar aprotic as well as non-polar solvents and EtOH-NaOH is established as the best solvent-base combination for the purpose. EtOH is found to be more effective than H_2O (A-Q and B-Q in Fig. 3), which may be attributed to the greater solubility of starting materials in EtOH than in H_2O. Optimization of NaOH added was carried out and an amount of 1.5 equivalent was established as the most suitable as it reduced the time requirement for complete consumption of **1** to 1 hour only. Work up was carried out to isolate the crude **3a**, which was then subjected to reductive cyclisation using alkaline $Na_2S_2O_4$ solution

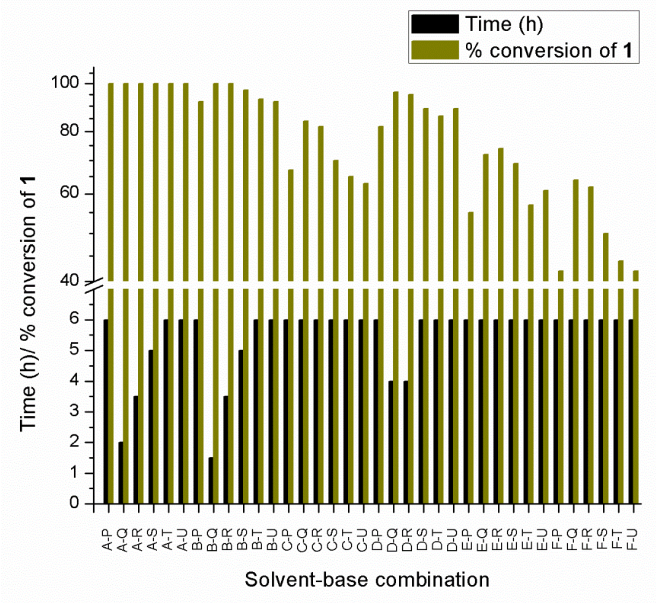
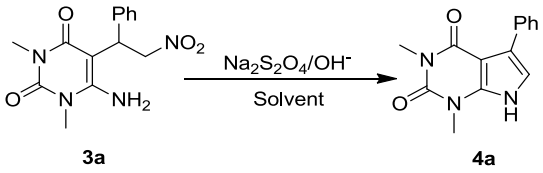


Figure 3. Bar diagram showing the effect of solvent-base combination on Scheme 3. Here, A=H_2O; B=EtOH; C=CH_3CN; D=DMF; E=CH_3COCH_3; F=$CHCl_3$; P=No base; Q=NaOH; R=Na_2CO_3; S=CH_3COONa; T=Et_3N; U=Ph_3P (% conversions were calculated from ^{1}H NMR spectra)



Scheme 4. Reductive cyclisation of Michael type adduct (**3a**)

(Scheme 4). Effect of solvent, stoichiometry of NaOH as base and temperature on the yield of product (**4a**) were also studied and the results are summarized in Table 1. Solvents like DMF, DMSO were not considered due to their high boiling point. Table 1 clearly indicates the suitability of EtOH and $(CH_3)_2CO$ for the purpose. However, EtOH became the first choice considering the fact that it was the most suitable solvent for the Scheme 3 too, which would offer the opportunity to carry out both Schemes 3 and 4 in a common solvent. The Table 1 also establishes 1:3:4 as the best stoichiometry for **3a**, $Na_2S_2O_4$ and NaOH as well as 60 ^{0}C as the optimum temperature for the reaction. After optimizing the reaction conditions for both Schemes 3and 4, an attempt was made to carry out the synthesis of pyrrolo[2,3-*d*]pyrimidine via a single pot two-steps route without isolating the intermediate Michael type product. Optimization for this overall route was also carried out which concluded with a reduction of the amount of NaOH added in the second step from 4 equivalent to 3.5 equivalent. The overall process has been expressed as Scheme 5.

The final product (**4a**) was confirmed as 1,3-dimethyl-5-phenyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione by single crystal X-ray analysis (Fig. 4).[14] Senda et al. reported the synthesis of the same compound (**4a**) in 1974 via a different route.[15] However, the compound synthesized by them might probably be some kind of structural isomer of **4a**, as we have observed clear mp difference (reported 287 ^{0}C; found 191 ^{0}C for

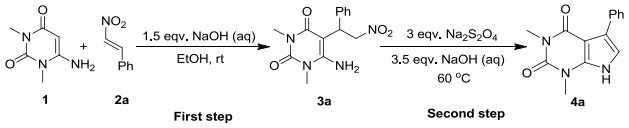
Table 1. Effect of reaction condition on **Scheme 4**

Entry	Solvent	**3a**:$Na_2S_2O_4$:NaOH	Temperature [°C]	Time [h]	% conversion of **3a** [%][a]	Yield [%][b]
1	H_2O	1:1:1	rt	6	32	32
			60	6	42	40
			reflux	6	48	45
		1:2:3	rt	6	45	43
			60	6	60	60
			reflux	6	64	57
		1:3:4	rt	6	46	45
			60	6	72	68
			reflux	6	80	72
		1:3:5	rt	6	48	46
			60	6	70	69
			reflux	6	82	67
2	EtOH	1:1:1	rt	6	30	30
			60	6	45	43
			reflux	6	58	52
		1:2:3	rt	6	43	40
			60	4	70	68
			reflux	4	75	70
		1:3:4	rt	6	60	58
			60	1	100	92
			reflux	1	100	84
		1:3:5	rt	6	62	56
			60	1	100	92
			reflux	1	100	86
3	CH_3CN	1:1:1	rt	6	25	25
			60	6	45	42
			reflux	6	55	53
		1:2:3	rt	6	50	48
			60	6	62	60
			reflux	6	63	62
		1:3:4	rt	6	52	50
			60	6	88	85
			reflux	6	88	82
		1:3:5	rt	6	54	52
			60	6	86	84
			reflux	6	90	85
4	$(CH_3)_2CO$	1:1:1	rt	6	35	32
			60	6	45	44
			reflux	6	55	53
		1:2:3	rt	6	40	36
			60	4	70	68
			reflux	4	75	70
		1:3:4	rt	6	65	63
			60	1	100	90
			reflux	0.5	100	86
		1:3:5	rt	6	65	63
			60	1	100	91
			reflux	0.5	100	79

[a]Calculated from ^{1}H NMR spectra.

[b]Isolated yield.

entry a, table 2 for example) between the two and our structure for **4a** has been supported by single crystal X-ray analysis. Contrary to our method, here, the 6-position of pyrimidine was targeted and then cyclisation. Although our method is a two-step process, still the same can be effected in a single pot. But, methodology adopted by Senda et el although is a two step process, but it is not one pot. Senda et al used tetralin as solvent



Scheme 5. One pot two- step synthesis of **4a**

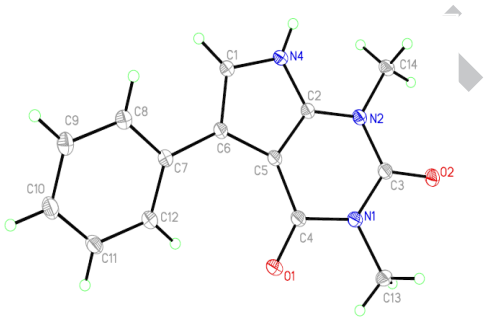


Figure 4. ORTEP diagram of **4a**

in many case, but we have not used any organic solvent for the reaction except in the work up procedure and purification.

The complete transformation can be studied by ^{1}H NMR spectra as shown in Fig. 5. To generalize the methodology, it was applied to a series of nitrostyrene derivatives (Scheme 6) and the results are summarized in Table 2.[16] Table 2 clearly reflects that the methodology is applicable to a wide variety of nitrostyrenes resulting in excellent to moderate yield. Presence of weakly electron withdrawing & electron donating groups (Entries **b, c, d** & **h**, Table 2) in the aromatic ring of the nitrostyrene derivatives

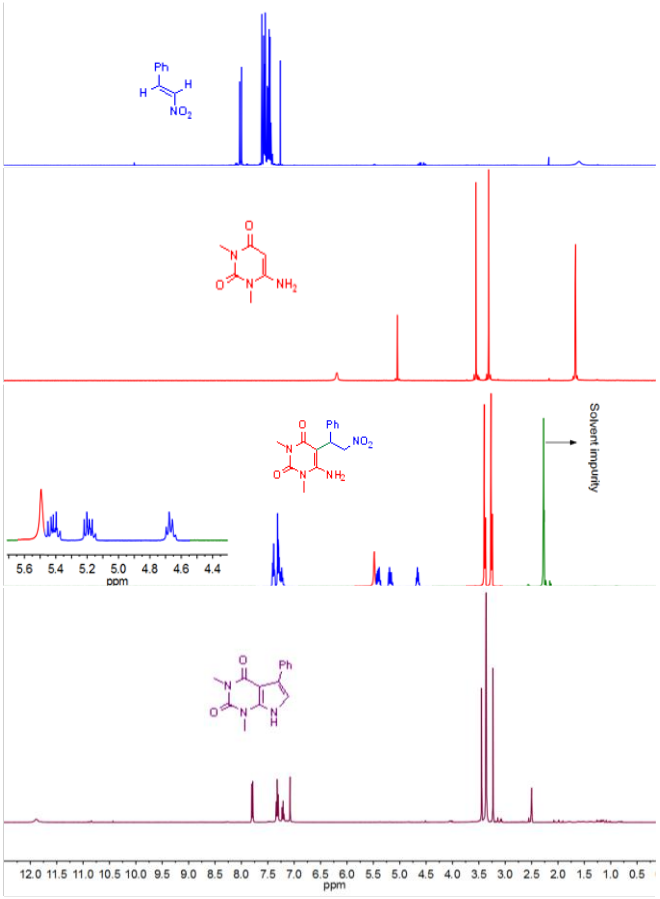
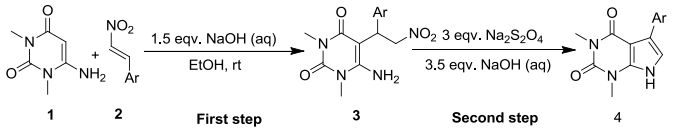


Figure 5. Comparison of ^{1}H NMR spectra of substrates, intermediate and product

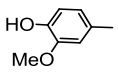
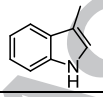
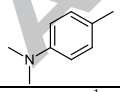
don't alter the yield of **4** to a great extent. However, the consumption of **1** as well as the yield of **4** is observed to be comparatively low in presence of strongly electron donating groups (Entries **I** & **k**, Table 2). Presence of heteroaryl units in the nitrostyrene derivatives also seemed to lower the yield of the final product **4** (Entries **e**, **f** & **j**, Table 2).



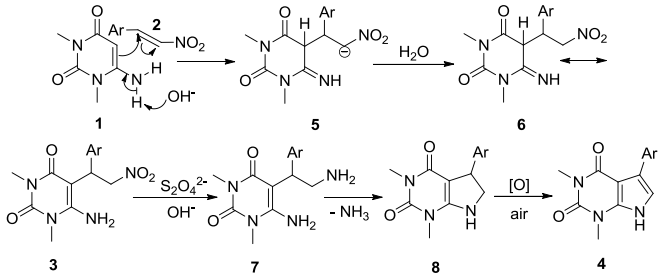
Scheme 6. General reaction scheme for synthesis of **4**

Although detailed mechanistic studies were not performed, a plausible mechanism has been suggested based on our observation towards Michael type addition reaction as well as literature reports available for reduction using alkaline $Na_2S_2O_4$ (Scheme 7). Once **7** is formed, it eliminatesone molecule of

Table 2. Synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives via **Scheme 6**

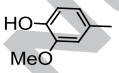
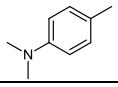
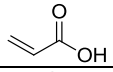
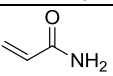
Entry	Ar in **2**&**4**	Time required for 1st step [h]	Conversion of **1** [%][a]	Timerequired for 2nd step [h]	Yield of **4** [%][b]	mp of **4** [°C]
a	C_6H_5-	1	100	1	92	191
b	*p*-ClC_6H_4-	1.5	100	1.2	87	227
c	*o*-HOC_6H_4-	1.5	100	2	82	278
d	*p*-$MeOC_6H_4$-	2	100	1.5	72	246
e		1.5	100	1.5	48	262
f		1.5	100	1.5	53	251
g		1.5	100	1	83	276
h	*p*-MeC_6H_4-	1.5	100	1	82	237
i		4	55	3	--	--
j		4	64	2	42	230
k		4	62	2	46	218

[a]Calculated from ^{1}H NMR spectra. [b]Isolated yield



Scheme 7. Plausible mechanism for the formation of **4**

Table 3. Michael type addition of **1** with electron deficient olefins via 1st step of **Scheme 6**

Entry	Ar in **2** & **4**	Time [h]	Conversion of **1** [%][a]	Yield of **3** [%][a]	mp of **3** [°C]
a	C_6H_5-	1	100	95	202
b	*p*-ClC_6H_4-	1.5	100	92	154
c	*o*-HOC_6H_4-	1.5	100	92	126
d	*p*-$MeOC_6H_4$-	2	100	88	242
e		1.5	100	64	195
f		1.5	100	62	191
g		1.5	100	88	137
h	*p*-MeC_6H_4-	1.5	100	86	202
i		4	55	38	216
j		4	64	54	160
k		4	62	54	195
l		6	--	--	--
m		6	--	--	--
n	PhCH=CHCOOH	6	--	--	--
o	PhCH=CHCOPh	6	--	--	--

[a]Calculated from ^{1}H NMR spectra.

[b]Isolated yield

Table 4. Bacterial zones of inhibition (in mm) by synthesized pyrrolo[2,3-*d*]pyrimidines

Entry	Compounds	Microorganisms			
		Gram positive		Gram negative	
		B. subtilis	*B. mycoides*	*E. coli*	*P. aeruginosa*
1	4a	-	-	-	-
2	4b	-	-	-	-
3	4c	-	-	-	-
4	4d	-	-	-	-
5	4e	20	-	12	18
6	4f	20	13	13	20
7	4g	18	17	14	20
8	4h	20	12	15	20
9	4j	20	-	12	20
10	4k	15	12	11	20

-, no inhibition zone

NH_3 to generate **8**, which undergoes aerial oxidation to result its aromatic counterpart **4**.

Being benefitted by the fastness of the methodology, we synthesized, isolated and characterized the Michael products (**3**) by stopping the reaction at the first step in a separate set of reactions. A few compounds of these series (**3a**, **3d** & **3k**) have already been reported,[17] however our methodology is found to be superior in most of the cases in terms of reaction condition (no dry methanol is required in our case) time and product yield. An attempt was made to extend the methodology for electron deficient olefins other than nitrostyrenes by taking acrylamide, acrylic acid, cinnamic acid and chalcone as electron deficient systems, but went in vain. The results are summarized in Table 3.[16]

The synthesized pyrrolo[2,3-*d*]pyrimidines (**4a-h, 4j** & **4k**) were screened for their in vitro antibacterial property against both Gram positive (*Bacillus subtilis* and *Bacillus mycoides*) and Gram negative (*E. coli*. and *Pseudomonous aeruginosa*) bacterial strains at a concentration of 5mg/ml by taking ampicillin (5 mg/mL) as reference compound.[16] The bacterial zones of inhibition (mm) values were evaluated using the well diffusion method and the results are summarized in Table 4. It is well noticed that some of the synthesized compounds (**4e-4h, 4j**&**4k**) showed remarkable activity against *P. aeruginosa* and *B. subtilis*.

In conclusion, a convenient one-pot, two-step synthesis of 5-arylpyrrolo[2,3-*d*]pyrimidines has been accomplished, which involves Michael type addition followed by reductive cyclisation of the adduct. The methodology is non-catalytic, however still attractive as it is quite general and covers a wide spectrum of nitrostyrenes. The methodology enjoys additional advantage of utilizing cheaper and easily available reagent system. From biological assay studies, it is found that six of the synthesized compounds show satisfactory activity against *P. aeruginosa* and *B. subtilis*.

Acknowledgment

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References and notes

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