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Solution-phase parallel synthesis of new 2*H*-pyrimido-[4,5-*e*][1,2,4]triazin-3-ylidenecyanamides

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Abstract—A practical synthesis of 2*H*-pyrimido[4,5-*e*][1,2,4]triazin-3-ylidenecyanamides has been developed. The key step is the coupling reaction of an aryldiazonium salt with 1-cyano-3-(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-2-methylisothiourea followed by intramolecular cyclization. A library of 2*H*-pyrimido[4,5-*e*][1,2,4]triazin-3-ylidenecyanamides was prepared in two steps from 6-aminouracils using this method.
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The solution-phase parallel synthesis of heterocyclic libraries is an attractive method for discovering biologically active compounds.[1] However, the construction of heterocyclic small-molecule libraries requires the development of new solution-phase synthetic methodologies. Since pyrimidotriazines exhibit various types of pharmacological activity, such as antibacterial, antiviral, and anticancer activities,[2] this skeleton is an attractive target for generating combinatorial libraries. There has been considerable interest in the 7-azapteridines (2*H*-pyrimido-[5,4-*e*][1,2,4]triazine ring system) because of their biological activity. Of particular interest has been the naturally occurring antibiotic 2-methylfervenulone (MSD-92, Fig. 1), which was isolated from fermentation broth of *Actinomycetes* and shown to have broad biological activities.[3] The synthesis and structural modification of MSD-92 has received growing attention over the past few decades.[4] Recently, derivatives of MSD-92 have been reported with inhibitory activity toward several protein tyrosine phosphatases[5] (PTPases). The 6-azapteridines (2*H*-pyrimido[4,5-*e*][1,2,4]triazine ring system) have also received attention because of antiviral activity and their structural similarity with pteridines or purines.[6] However, only a few synthetic routes to 6-azapteridines from the appropriate pyrimidine precursors have been reported.[6a,d] Synthesis of one of the 6-azapteridines, 2*H*-pyrimido[4,5-*e*][1,2,4]triazine **1** was achieved using either photo-induced or thermally induced (210 °C) cyclization.[6f] The replacement of a urea or thiourea by a cyanoguanidine group is a recognized method of increasing the biological activity of drug-like compounds.[7,8] We focused our efforts on the synthesis of a new 2*H*-pyrimido[4,5-*e*][1,2,4]triazin-3-ylidenecyanamide system **2** that would incorporate *N*-cyanoimino group as an isosteric replacement of the urea in **1**.

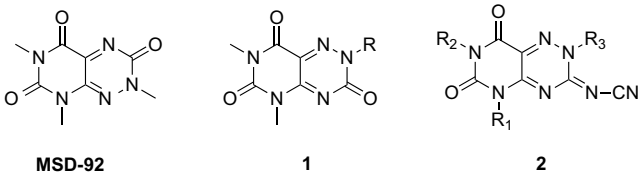

Figure 1.

Here, we report a new method for synthesizing the 2*H*-pyrimido[4,5-*e*][1,2,4]triazine skeleton **5** by coupling an aryldiazonium salt with 1-cyano-3-(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-2-methylisothioureas **4**, followed by intramolecular cyclization[4b,9] with the elimination of methanethiol at room temperature. We

Keywords: 2*H*-Pyrimido[4,5-*e*][1,2,4]triazin-3-ylidenecyanamides; Pyrimidotriazine; Solution-phase parallel synthesis.
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used this route to construct a library of 2*H*-pyrimido[4,5-*e*][1,2,4]triazine compounds.

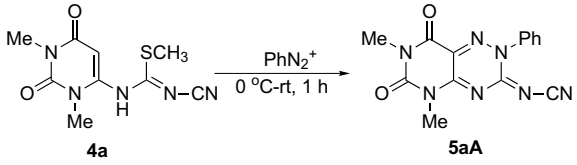
In our synthetic approach for preparing pyrimidotriazines **5**, the key intermediate, 1-cyano-3-(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-2-methylisothiourea **4a**, was obtained from 6-aminouracil **3a**. 6-Amino-1,3-dimethyluracil **3a** and dimethyl *N*-cyanodithioimidocarbonate was heated in DMF at 130 °C for 5 h in the presence of K_2CO_3.[10] After concentrating this reaction mixture, it was purified by recrystallization from water and EtOH to provide the previously unknown compound **4a** as a white solid in 77% isolated yield.

5-Phenylazouracils are intermediates in the synthesis of various heterocycles containing the uracil moiety.[11] We applied the phenyldiazonium salt coupling to our intermediate **4a** to synthesize a diverse library of pyrimidotriazines **5** via cyclization of 5-phenylazouracil in a one-pot process.

The phenyldiazonium salt was coupled with **4a** under the conditions shown in Table 1. The yield of **5aA** was influenced by the solubility of **4a**. Generally, the starting material **4a** was dissolved in relatively polar aprotic solvents. When we initially tried the coupling reaction of 1.5 equiv of phenyldiazonium salt with **4a** in acetonitrile (entry 1), significant amounts of starting material was recovered. To generate the phenyldiazonium salt, the procedure using $NaNO_2$ in water, HCl, and aniline in EtOH was the most practical one, followed by the reaction in DMF to provide **5aA** in 53% isolated yield (entry 4). Similarly, using DMSO instead of DMF increased the yield of **5aA** by 10% due to the increased solubility of **4a** in DMSO. Further optimization used a 3-fold molar excess of phenyldiazonium chloride, generated in situ from the reaction of aniline with $NaNO_2$ and HCl in water and EtOH, coupled with **4a** in DMSO to give **5aA** in 77% yield (entry 6). When we changed the generation method of the phenyldiazonium salt to isobutyl nitrite, the yield of **5aA** was acceptable at 73% (entry 7).

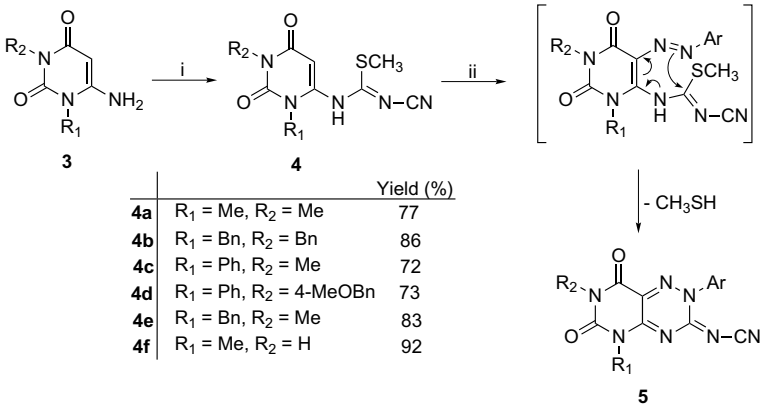
To prepare a combinatorial library of pyrimidotriazines **5**, new compounds **4b–f** were readily obtained from the corresponding 6-aminouracils **3b–f** and dimethyl *N*-cyanodithioimidocarbonate by heating in DMF at 130 °C for 3–5 h, in 72–92% yields, as shown in Scheme 1. Of the 6-aminouracils **3a–f**, **3a**, and **3f** were commercially available and **3b–e** were prepared from the corresponding urea using a known method.[12] The 6-aminouracil **3d** has not been previously reported.

Table 1. Optimization studies for the synthesis of **5aA**



Entry	Phenyldiazonium salt (solvent ratio)	Equiv	Solvent	Yield (%)
1	*i*-BuONO, HCl/EtOH–acetone (1:1)	1.5	CH_3CN	15 [54][a]
2	*i*-BuONO, HCl/EtOH–acetone (1:1)	1.5	DMF	45
3	*i*-BuONO, TFA/CH_2Cl_2–CH_3CN (2:1)	1.5	DMF	47
4	$NaNO_2$, HCl/EtOH–H_2O (2:1)	1.5	DMF	53
5	$NaNO_2$, HCl/EtOH–H_2O (2:1)	1.5	DMSO	63
6	$NaNO_2$, HCl/EtOH–H_2O (2:1)	3.0	DMSO	77
7	*i*-BuONO, TFA/CH_2Cl_2–CH_3CN (2:1)	3.0	DMSO	73

[a] Recovered starting material.



		Yield (%)
4a	R_1 = Me, R_2 = Me	77
4b	R_1 = Bn, R_2 = Bn	86
4c	R_1 = Ph, R_2 = Me	72
4d	R_1 = Ph, R_2 = 4-MeOBn	73
4e	R_1 = Bn, R_2 = Me	83
4f	R_1 = Me, R_2 = H	92

Scheme 1. Reagents and conditions: (i) dimethyl *N*-cyanodithioimidocarbonate, K_2CO_3, DMF, 130 °C, 5 h; (ii) ArN_2^+, DMSO, 0 °C to rt, 1 h.

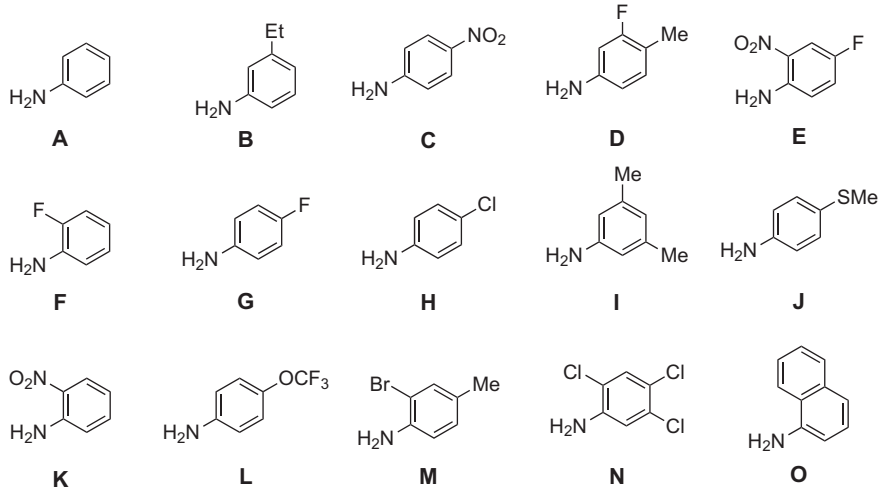


Figure 2. Anilines used for preparing the pyrimidotriazines **5**.

Table 2. 2*H*-Pyrimido[4,5-*e*][1,2,4]triazin-3-ylidenecyanamide **5**[a] array (isolation yields and purities[b])

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
4a	**5aA**	**5aB**	**5aC**	**5aD**	**5aE**	**5aF**	**5aG**	**5aH**	**5aI**	**5aJ**	**5aK**	**5aL**	**5aM**	**5aN**	**5aO**
	77(94)	72(85)	65(91)	42(92)	54(91)	52(87)	58(96)	78(96)	42(87)	45(82)	42(83)	68(92)	55(87)	62(82)	55(90)
4b	**5bA**	**5bB**	**5bC**	**5bD**	**5bE**	**5bF**	**5bG**	**5bH**	**5bI**	**5bJ**	**5bK**	**5bL**	**5bM**	**5bN**	**5bO**
	70(92)	68(95)	85(83)	50(83)	72(87)	62(88)	42(95)	52(93)	63(93)	52(94)	52(84)	72(96)	67(82)	62(92)	53(85)
4c	**5cA**	**5cB**	**5cC**	**5cD**	**5cE**	**5cF**	**5cG**	**5cH**	**5cI**	**5cJ**	**5cK**	**5cL**	**5cM**	**5cN**	**5cO**
	65(87)	65(94)	52(94)	65(92)	65(93)	43(91)	36(94)	42(91)	52(91)	47(85)	45(91)	47(84)	45(85)	65(84)	62(84)
4d	**5dA**	**5dB**	**5dC**	**5dD**	**5dE**	**5dF**	**5dG**	**5dH**	**5dI**	**5dJ**	**5dK**	**5dL**	**5dM**	**5dN**	**5dO**
	45(92)	52(97)	48(87)	65(94)	62(91)	62(90)	45(85)	67(88)	76(94)	72(93)	54(96)	58(92)	52(90)	47(94)	47(94)
4e	**5eA**	**5eB**	**5eC**	**5eD**	**5eE**	**5eF**	**5eG**	**5eH**	**5eI**	**5eJ**	**5eK**	**5eL**	**5eM**	**5eN**	**5eO**
	69(95)	61(91)	52(95)	42(95)	44(89)	42(92)	62(87)	51(95)	42(93)	32(86)	54(91)	45(91)	56(88)	55(88)	51(94)
4f	**5fA**	**5fB**	**5fC**	**5fD**	**5fE**	**5fF**	**5fG**	**5fH**	**5fI**	**5fJ**	**5fK**	**5fL**	**5fM**	**5fN**	**5fO**
	61(93)	47(92)	46(94)	43(87)	42(92)	35(87)	51(96)	51(92)	42(85)	43(88)	32(81)	45(92)	54(90)	42(92)	47(95)

[a] Reaction conditions: **5aA–5aO**, **5bA–5bO**, **5cA–5cO**, **5dA–5dO**, and **5eA–5eO** were obtained by condition of entry 6 in Table 1 ($NaNO_2$, HCl, DMSO, EtOH, H_2O). **5fA–5fO** were obtained by condition of entry 7 in Table 1 (*i*-BuONO, DMSO, CH_2Cl_2, CH_3CN).
[b] % Purity based on NMR and LCMS analysis.

We prepared various pyrimidotriazines **5** by parallel synthesis from **4a–f** and anilines **A–O** (15 compounds, Fig. 2) as shown in Table 2. Due to the good yield, the reaction condition of entry 6 in Table 1 was initially chosen as the standard procedure. The coupling reaction of **4a** and the aryldiazonium chloride salts from the 15 anilines in Figure 2 using the Bohdan Miniblock system afforded the expected 2*H*-pyrimido[4,5-*e*][1,2,4]triazin-3-ylidenecyanamides **5aA–5aO** in acceptable yields without any apparent steric or electronic effect of substituents on the aromatic ring.[13] Similarly, when we investigated the influence of the structure of *N*-1,3-disubstituted uracils **4b–e** with the same procedure, the desired products of **5bA–5eO** were isolated in moderate yields and high purities. This method is applicable to the *N*-3 unsubstituted uracil **4f**, where the hydrogen at the *N*-3 position mimics that of uracil derivatives and their nucleosides, this being essential for hydrogen bonding with purine bases in biology.[14] For the reaction of **4f** with phenyldiazonium chloride salts using the procedure described above, only **5fA** was isolated, and in only 36% yield. To improve the solubility of **4f** in the solvent system, we tried to generate the phenyldiazonium salt using isobutyl nitrite in the aprotic solvent CH_3CN and CH_2Cl_2 (entry 7 in Table 1). Under this condition, **4f** in DMSO gave **5fA** in 61% yield. With this procedure, the parallel synthesis of compounds **5fA–5fO** was achieved by coupling **4f** with aryldiazonium salts (**A–O**) as shown in Table 2.

In summary, we have developed a highly efficient and mild synthetic method for the preparation of the pyrimidotriazine system starting from 6-aminouracils in two steps. The coupling reaction of **4**, obtained from the reaction of 6-aminouracil **3** with dimethyl *N*-cyanodithioimidocarbonate in DMF on heating at 130 °C, with several aryldiazonium salts proceeded via intramolecular cyclization to produce the corresponding pyrimidotriazine adducts **5** at room temperature. A library of new 2*H*-pyrimido[4,5-*e*][1,2,4]triazin-3-ylidenecyanamides **5** (90 compounds) was constructed using solution-phase synthesis. Currently, efforts to expand the

scope of the method in combination with its application to the synthesis of pharmaceutical molecules are ongoing in our laboratory.

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References and notes

1. An, H.; Dan Cook, P. *Chem. Rev.* **2000**, *100*, 3311–3340.
2. (a) Boyle, P. H., 2nd ed. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: New York, 1996; Vol. 7, pp 785–840; (b) Tayler, E. C.; Pont, J. L.; Warner, J. C. *J. Org. Chem.* **1988**, *53*, 3568–3572, and reference cited therein.
3. (a) Taylor, E. C.; Sowinski, F. *J. Am. Chem. Soc.* **1969**, *91*, 2143–2144; (b) Taylor, E. C.; Sowinski, F. *J. Org. Chem.* **1975**, *40*, 2321–2329; (c) Ichiba, M.; Nishigaki, S.; Senga, K. *J. Org. Chem.* **1978**, *43*, 469–472; (d) Wang, H.; Lim, K. L.; Yeo, S. L.; Xu, X.; Sim, M. M.; Ting, A. E.; Wang, Y.; Yee, S.; Tan, Y. H.; Pallen, C. J. *J. Nat. Prod.* **2000**, *63*, 1641–1646.
4. (a) Taylor, E. C.; Sowinski, F. *J. Am. Chem. Soc.* **1968**, *90*, 1374–1375; (b) Nagamatsu, T.; Yamasaki, H.; Yoneda, F. *Heterocycles* **1994**, *37*, 1147–1164; (c) Mehrotra, M. M.; Sternbach, D. D.; Rutkowske, R. D.; Feldman, P. L. *J. Org. Chem.* **1995**, *60*, 7063–7065.
5. Guertin, K. R.; Setti, L.; Qi, L.; Dunsdon, R. M.; Dymock, B. W.; Jones, P. S.; Overton, H.; Taylor, M.; Williams, G.; Sergi, J. A.; Wang, K.; Peng, Y.; Renzetti, M.; Boyce, R.; Falcioni, F.; Garippa, R.; Olivier, A. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2895–2898.
6. (a) Heinisch, L.; Ozegowski, W.; Muhlstadt, M. *Chem. Ber.* **1964**, *97*, 5–15; (b) Taylor, E. C.; Morrison, R. W., Jr. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 312; (c) Taylor, E. C., Jr.; Morrison, R. W., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1976–1979; (d) Yoneda, F.; Higuchi, M.; Nagamatsu, T. *J. Am. Chem. Soc.* **1974**, *96*, 5607–5608; (e) Taylor, E. C.; Martin, S. F. *J. Org. Chem.* **1970**, *35*, 3792–3795; (f) Yoneda, F.; Higuchi, M. *Chem. Pharm. Bull.* **1977**, *25*, 2794–2796; (g) Huang, J. J. *J. Org. Chem.* **1985**, *50*, 2293–2298.
7. (a) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R. *J. Med. Chem.* **1977**, *20*, 901–906; (b) Jadhav, P. K.; Woerner, F. J.; Lam, P. Y. S.; Hodge, C. N.; Eyermann, C. J.; Man, H.-W.; Daneker, W. F.; Bacheler, L. T.; Rayner, M. M.; Meek, J. L.; Erickson-Viitanen, S.; Jackson, D. A.; Calabrese, J. C.; Schadt, M.; Chang, C.-H. *J. Med. Chem.* **1998**, *41*, 1446–1455; (c) Cooper, A. B.; Strickland, C. L.; Wang, J.; Desai, J.; Kirschmeier, P.; Patton, R.; Bishop, W. R.; Weber, P. C.; Girijavallabhan, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 601–605; (d) Matsuno, K.; Nakajima, T.; Ichimura, M.; Giese, N. A.; Yu, J.-C.; Lokker, N. A.; Ushiki, J.; Ide, S.-I.; Oda, S.; Nomoto, Y. *J. Med. Chem.* **2002**, *45*, 4513–4523.
8. (a) Schou, C.; Ottosen, E. R.; Peterson, H. J.; Bjorkling, F.; Latini, S.; Hjarnaa, P. V.; Bramm, E.; Binderup, L. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3095–3100; (b) Ekelund, S.; Nygren, P.; Larsson, R. *Bioorg. Biochem. Pharcol.* **2001**, *61*, 1183–1193; (c) Chern, J.-H.; Shia, K.-S.; Chang, C.-M.; Lee, C.-C.; Lee, Y.-C.; Tai, C.-L.; Lin, Y.-T.; Chang, C.-S.; Tseng, H.-Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1169–1172.
9. (a) Pfleiderer, W.; Blankenhorn, G. *Tetrahedron Lett.* **1969**, *10*, 4699–4702; (b) Fusco, R.; Sannicolo, F. *Tetrahedron Lett.* **1982**, *23*, 1829–1830.
10. Tominaga, Y. T.; Kohra, S.; Okuda, H.; Ushirogochi, A.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1984**, *32*, 122–129.
11. (a) Pfleiderer, W.; Nubel, G. *Chem. Ber.* **1960**, *93*, 1406–1416; (b) Senga, K.; Kanamori, Y.; Nishigaki, S. *Heterocycles* **1978**, *9*, 1437–1439; (c) Yoneda, F.; Koga, R. *Heterocycles* **1981**, *16*, 2137–2140; (d) Nishigaki, S.; Misuzu, F.; Senga, K. J. *Heterocycl. Chem.* **1982**, *19*, 769–773.
12. Papesch, V.; Schroeder, E. F. *J. Org. Chem.* **1951**, *16*, 1879.
13. General procedure for the parallel synthesis of **5aA**–**5aO**: On the Mettler-Toledo Miniblock synthesizer, a stirred solution of anilines (**A**–**O**, 0.72 mmol, 15 compounds) in EtOH (0.4 mL) was cooled to 0 °C. After addition of HCl (0.14 mL, 0.72 mmol) to the reaction mixtures, then a solution of sodium nitrite (0.2 mL, 0.36 M in H_2O) was slowly added. After 30 min, to this solution was added 1-cyano-3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)-2-methylisothiourea **4a** (0.8 mL, 0.3 M in DMSO) at 0 °C. The blocks were shaken for 1 h at 25 °C. The reaction mixture was concentrated under reduced pressure in a Genevac HT-4X. The residue was purified on a Biotage Quad 3^+ using a flash 12 M using ethyl acetate and hexane solvent. **5aA**: (58 mg, 77%). Mp = 290–292 °C (decomposition). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.53 (s, 5H), 3.68 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.9, 155.4, 150.9, 149.3, 140.1, 130.3, 129.3, 125.6, 124.2, 114.0, 29.9, 29.2. IR (cm^{-1}): 2192, 1697, 1654, 1571. LCMS (*m*/*z*): 309.
14. (a) Watson, J. D.; Hopkins, N. H.; Roberts, J. W.; Steitz, J. A.; Weiner, A. M. *Molecular Biology of the Gene*, 4th ed.; Benjamin: Menlo Park, CA, 1987; (b) Voet, D.; Voet, J. G. *Biochemistry*; Wiley: New York, 1990; (c) Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Watson, J. D. *Molecular Biology of the Cell*, 3rd ed.; Garland: New York, 1994.