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A tandem decarboxylation/Diels–Alder reaction of 5-amino-1-phenyl-4-pyrazolecarboxylic acid with 1,3,5-triazines

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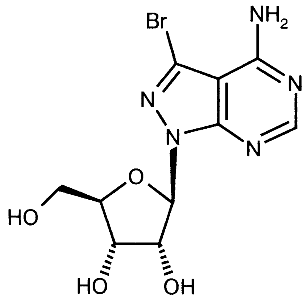
Abstract—A tandem decarboxylation/Diels–Alder reaction of 5-amino-1-phenyl-4-pyrazolecarboxylic acid with various 1,3,5-triazines was reported. The dienophile, 5-amino-1-phenylpyrazole, was generated in situ via decarboxylation and immediately trapped by 1,3,5-triazines leading to 4,6-disubstituted 1-phenylpyrazolo[3,4-*d*]pyrimidines in one step.

Many drug discovery efforts have been directed at the regulation of purine metabolic pathways and functions of purinergic receptors. Consequently, purine analogues are extensively exploited as potential therapeutics.[1] Since pyrazolo[3,4-*d*]pyrimidine is isomeric with purine, its analogues are often synthesized and studied for their biological activities related to purine metabolic pathways and purinergic receptors. For example, GP515 is a potent adenosine kinase inhibitor (IC_{50} = 4.6 nM),[2] and 2′-(4-amino-1-phenylpyrazolo[3,4-*d*]pyrimidin-6-ylthio)-(*N*-ethyl)ethanamide (**1**)[3] is a potent ligand at the A_1 receptor (K_i = 12 nM) (Fig. 1).

Our interest in adenosine regulating agents directed us to study efficient synthetic methodologies for various purine analogues.[4] Such efforts led to the introduction of 5-aminopyrazoles as dienophiles in the Diels–Alder reaction with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine for the one-step synthesis of pyrazolo[3,4-*d*]pyrimidines,[5] and recently a tandem decarboxylation/Diels–Alder (TDDA) reaction of various 5-amino-4-imidazolecarboxylic acids with 1,3,5-triazines for the one-step synthesis of purine analogues.[6] We envisioned that the TDDA reaction can be extended to 5-amino-4-pyrazolecarboxylic acids, which should allow those otherwise unreactive pyrazoles to serve as productive dienophiles. Herein, we report the TDDA reaction of 5-amino-1-phenyl-4-pyrazolecarboxylate (**2**)[7] with various 1,3,5-triazines (**3a**–**h**)[8] under both mild thermal and Lewis acid conditions. This method is useful for the one-step synthesis of various 4,6-disubstituted 1-phenylpyrazolo[3,4-*d*]pyrimidines.

Previously, 1,3,5-triazine **3a** was shown to be a reactive diene with 5-aminopyrazoles as the dienophiles, and it was proven to participate in the TDDA reaction of



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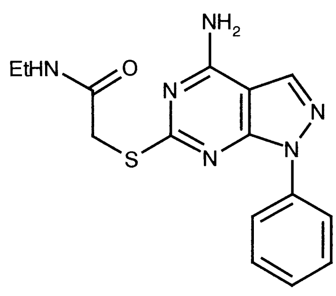

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Figure 1.

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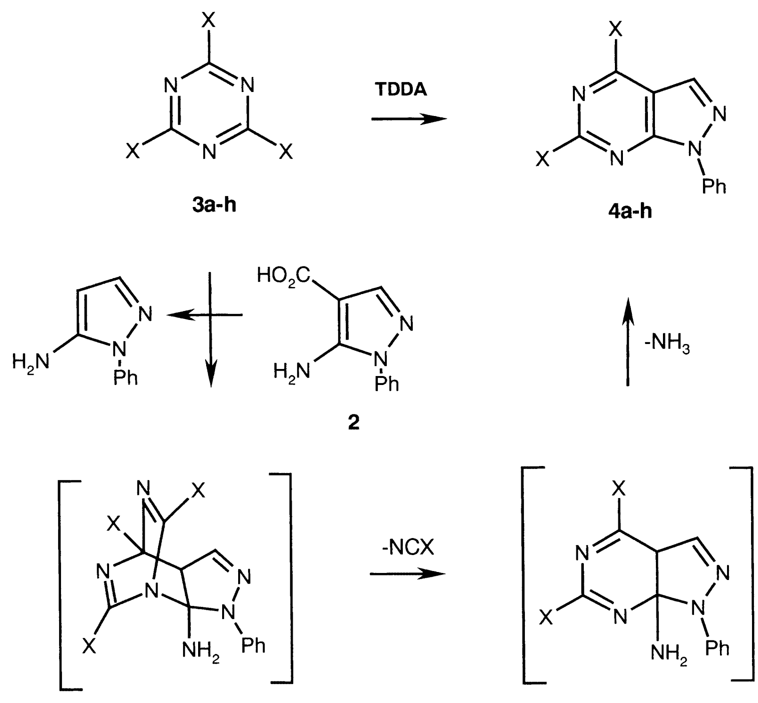
pyrazole **2** as well. Thus, heating a mixture of **2** and **3a** (90°C, DMF–AcOH) generated 4,6-bis(ethoxycarbonyl)-1-phenylpyrazolo[3,4-*d*]pyrimidine (**4a**) in high yield (83%).[9] This TDDA reaction appears to be acid-mediated, since no **4a** was detected with only starting materials being recovered when the sodium salt of **2** was used in the absence of an acid (Table 1, entry 2).[10] Such observation suggests that the decarboxylation of **2** precedes the [4+2] cycloaddition reaction and **2** itself is not reactive enough to participate in the [4+2] cycloaddition reaction with **3a**. This result is consistent with our observations from the TDDA reaction of 5-amino-4-imidazolecarboxylic acids with 1,3,5-triazines. It is surprising that under the same reaction conditions, **2** was only slowly converted to 5-amino-1-phenylpyrazole (60%, DMF–AcOH, 95°C, 56 h), even though the current TDDA reaction of **3a** and **2** was done quickly (in 2 h). This suggests that current TDDA reaction conditions appeared to accelerate the decarboxylation of **2** possibly via trapping of the in situ generated 5-amino-1-phenylpyrazole by **3a**. A reaction mechanism analogous to our previous observations is envisioned (Scheme 1).[11] Decarboxylation of **2** gave 5-amino-1-phenylpyrazole that was subsequently trapped by **3a** through a [4+2] cycloaddition reaction, and then the resulting cycloadduct underwent a retro Diels–Alder reaction with the loss of ethyl cyanoformate followed by final aromatization with loss of ammonia to regioselectively produce **4a**. Other 1,3,5-triazines (**3b–d**) with electron-withdrawing substituents generated the corresponding pyrazolo[3,4-*d*]pyrimidines (**4b–d**) in high yields as well (Table 1, entries 3–5). The parent 1,3,5-

Table 1. Tandem decarboxylation/Diels–Alder reactions of pyrazole **2** with 1,3,5-triazines **3a–h**

Entry	Diene	X=	Conditions[a]	Product	Yield (%)
1	**3a**	CO_2Et	DMF–AcOH, 90°C, 2 h	**4a**	83
2	**3a**	CO_2Et	DMF, 90°C, 48 h	**4a**	0[b,c]
3	**3b**	CO_2Me	DMF–AcOH, 95°C, 3.5 h	**4b**	87
4	**3c**	CF_3	DMF–AcOH, 90°C, 2 h	**4c**	78
5	**3d**	CF_2Cl	DMF–AcOH, 95°C, 4.5 h	**4d**	70
6	**3e**	$PO(OEt)_2$	DMF–AcOH, 95°C, 3 h	**4e**	10[d]
7	**3f**	H	DMF–AcOH, 100°C, 48 h	**4f**	0[c]
8	**3f**	H	DMSO, $BF_3{\cdot}OEt_2$, 100°C, 3 h	**4f**	64
9	**3g**	Ph	DMF–AcOH, 100°C, 48 h	**4g**	0[c]
10	**3g**	Ph	DMSO, $BF_3{\cdot}OEt_2$, 100°C, 48 h	**4g**	0[c]
11	**3h**	SMe	DMF–AcOH, 100°C, 48 h	**4h**	0[c]
12	**3h**	SMe	DMSO, $BF_3{\cdot}OEt_2$, 100°C, 48 h	**4h**	0[c]

[a] Reactions were conducted using sodium salt of **2** (2 equiv) and **3a–h**.
[b] DMF was the sole solvent.
[c] Unreacted 1,3,5-triazine was recovered.
[d] No unreacted 1,3,5-triazine was detected.



Scheme 1. X groups: (**a**) EtO_2C; (**b**) MeO_2C; (**c**) F_3C; (**d**) ClF_2C; (**e**) $(EtO)_2OP$; (**f**) H; (**g**) Ph; (**h**) MeS.

triazine (**3f**) and those 1,3,5-triazines (**3g** and **3h**) with electron-donating substituents, however, did not give the corresponding pyrazolo[3,4-*d*]pyrimidines (**4f–h**) under thermal conditions (Table 1, entries 7, 9 and 11). It is somewhat surprising that the reaction between **2** and **3e** gave the corresponding pyrazolo[3,4-*d*]pyrimidines (**4e**) only in low yield despite the presence of electron-withdrawing substituents (-P(O)(OEt)$_2$) on the 1,3,5-triazine. The fact that no **3e** was detected suggested that either **3e** and/or **4e** were not stable under the reaction conditions or the conversion of the initial [4+2] cycloadduct to **4e** was not complete under current conditions.

Although mineral acids have been shown to facilitate inverse electron-demand Diels–Alder reactions,[12] the presence of acetic acid under the current reaction conditions was not enough to promote reactions for 1,3,5-triazine **3f–h**. We decided to investigate the effect of Lewis acids on the current TDDA reactions, and when the reaction between **2** and **3f** was conducted in the presence of $BF_3 \cdot OEt_2$, the desired TDDA product **4f** was isolated in good yield (64%, Table 1, entry 8).[13] However, preliminary studies showed that, even in the presence of $BF_3 \cdot OEt_2$, 1,3,5-triazines **3g** and **3h** were not reactive enough to participate in the current TDDA reactions (Table 1, entries 10 and 12).

In summary, we have demonstrated that TDDA reactions of 5-amino-1-phenyl-4-pyrazolecarboxylic acid with various electron-deficient 1,3,5-triazines (**3a–e**) under mild thermal conditions allow the one-step syntheses of highly substituted pyrazolo[3,4-*d*]pyrimidines in excellent yields. Moreover, in a preliminary study a Lewis acid ($BF_3 \cdot OEt_2$) was shown, for the first time, to facilitate inverse electron-demand Diels–Alder reaction of 1,3,5-triazine (**3f**). In addition, four new 1,3,5-triazines **3b–e** were introduced as productive heteroaromatic dienes for inverse electron-demand Diels–Alder reactions. It is anticipated that TDDA reactions could introduce a new set of productive dienophiles, which normally are deactivated (by the presence of an electron-withdrawing group (-CO_2R)) towards inverse electron-demand Diels–Alder reactions, for the 1,3,5-triazine Diels–Alder reactions. Moreover, the current TDDA reaction may be more useful in the case of a thermally unstable dienophile since it will be generated in situ and immediately trapped by 1,3,5-triazines.

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8. (a) Compounds **3a**, **3b** and **3h** were prepared according Boger's procedure. See: Boger, D. L.; Dang, Q. *Tetrahedron* **1988**, *44*, 3379; (b) Compound **3e** was prepared according to Morrison's procedure. See: Morrison, D. C. *J. Org. Chem.* **1957**, *22*, 444; (c) Compounds **3c**, **3f**, and **3g** were purchased from Aldrich, and **3d** was purchased from Lancaster.
9. Representative procedures for the thermal TDDA reaction: A mixture of **2** (225 mg, 1 mmol) and **3a** (150 mg, 0.5 mmol) in anhydrous DMF–AcOH (1:1) was heated at 90°C under nitrogen for 2 h. The cooled reaction mixture was evaporated to dryness, and the residue was purified by flash chromatography (SiO_2, 2×15 cm, 30% EtOAc–hexane) to give 4,6-bis(ethoxycarbonyl)-1-phenylpyrazolo[3,4-*d*]pyrimidine (**4a**) as a sticky solid (170 mg, 83%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.80 (1H, s), 8.28 (2H, m), 7.57 (2H, m), 7.39 (1H, m), 4.62 (2H, q, $J=7.4$ Hz), 4.57 (2H, q, $J=7.4$ Hz), 1.54 (3H, t, $J=7.4$ Hz), 1.49 (3H, t, $J=7.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.38, 163.30, 154.21, 154.09, 150.48, 138.16, 135.37, 129.51, 127.57, 121.55, 114.76, 63.24, 63.01, 14.13; MS calcd for $C_{17}H_{16}N_4O_4+H^+$: 341, found 341. Anal. calcd for $C_{17}H_{16}N_4O_4 \cdot 0.25H_2O$: C, 59.21; H, 4.82; N, 16.25. Found: C, 59.29; H, 4.72; N, 16.19%.
   4,6-Bis(methoxycarbonyl)-1-phenylpyrazolo[3,4-*d*]pyrimidine (4b). Flash chromatography (SiO_2, 2×15 cm, 30% EtOAc–hexane) gave **4b** as a sticky solid (160 mg, 87%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.83 (1H, s), 8.29 (2H, m), 7.60 (2H, m), 7.41 (1H, m), 4.19 (3H, s), 4.15 (3H, s); MS calcd for $C_{15}H_{12}N_4O_4+H^+$: 313, found 313. Anal. calcd for $C_{15}H_{12}N_4O_4 \cdot 0.11$EtOAc: C, 57.60; H, 4.03; N, 17.40. Found: C, 57.53; H, 3.73; N, 17.02%.
   4,6-Bis(trifluoromethyl)-1-phenylpyrazolo[3,4-*d*]pyrimidine (4c). Flash chromatography (SiO_2, 2×15 cm, 10%

EtOAc–hexane) gave **4c** as a solid (181 mg, 78%). mp 104–105°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.59 (1H, s), 8.23 (2H, m), 7.61 (2H, m), 7.46 (1H, m); MS calcd for $C_{13}H_6N_4F_6$+H^+: 333, found 333. Anal. calcd for $C_{13}H_6F_6N_4$: C, 47.00; H, 1.82; N, 16.87. Found: C, 47.22; H, 1.74; N, 16.78%.

4,6-Bis(chlorodifluoromethyl)-1-phenylpyrazolo[3,4-*d*]pyrimidine (4d). Flash chromatography (SiO_2, 2×15 cm, 10% EtOAc–hexane) gave **4d** as a solid (67 mg, 70%). mp 104–106°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.58 (1H, s), 8.21 (2H, m), 7.80 (2H, m), 7.42 (1H, m); MS calcd for $C_{13}H_6N_4Cl_2F_4$+H^+: 366, found 366. Anal. calcd for $C_{13}H_6Cl_2F_4N_4$: C, 42.77; H, 1.66; N, 15.34. Found: C, 42.80; H, 1.51; N, 15.26%.

4,6-Bis(diethylphosphono)-1-phenylpyrazolo[3,4-*d*]pyrimidine (4e). Flash chromatography (SiO_2, 2×15 cm, 70% EtOAc–hexane) gave **4e** as a hard gel (13 mg, 10%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.78 (1H, s), 8.25 (2H, m), 7.58 (2H, m), 7.40 (1H, m); MS calcd for $C_{19}H_{26}N_4O_6P_2$+ Na^+: 491, found 491. Anal. calcd for $C_{19}H_{26}N_4O_6P_2$: C, 48.72; H, 5.60; N, 11.96. Found: C, 48.72; H, 5.24; N, 12.15%.

10. When the ethyl ester of **2** was subjected to the current TDDA conditions (DMF–AcOH, 90°C, 15 h), as suggested by a referee, no [4+2] cycloaddition was observed with only starting materials being recovered.
11. For a theoretical study on Diels–Alder reactions between various five-membered aromatic heterocycles and 1,3,5-triazine, see: Yu, Z.-X.; Dang, Q.; Wu, Y.-D. *J. Org. Chem.* **2001**, *66*, 6029.
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13. General procedure for Lewis acid-promoted TDDA reactions. A mixture of **2** (100 mg, 0.5 mmol), **3f** (20 mg, 0.25 mmol) and $BF_3 \cdot OEt_2$ (42 mg, 0.3 mmol) in anhydrous DMSO was heated at 100°C under nitrogen for 3 h. The cooled reaction mixture was diluted with ethyl acetate (50 mL), washed with 0.1 M NaOH (2×30 mL), water (30 mL), brine (15 mL), dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (SiO_2, 2×15 cm, 30% EtOAc–hexane) to give 1-phenylpyrazolo[3,4-*d*]pyrimidine (**4f**) as a yellow solid (31 mg, 64%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.27 (1H, s), 9.13 (1H, s), 8.33 (1H, s), 8.26–7.33 (5H, m), 7.39 (1H, m). Anal. calcd for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.24; H, 4.14; N, 28.44%.