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# A tandem decarboxylation and inverse electron-demand Diels–Alder reaction of amino-thiophenecarboxylic acids with 1,3,5-triazines

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ABSTRACT

The scope of 1,3,5-triazine inverse electron-demand Diels–Alder (IDA) reactions was expanded to include aminothiophenecarboxylic acids as latent dienophiles. A series of 2-amino-3-thiophenecarboxylic acids (**1a–d**) and a 3-amino-2-thiophenecarboxylic acid (**5**) were introduced as productive dienophiles in IDA reactions with various 1,3,5-triazines (**2a–e**). This method is useful for the one-step synthesis of both thieno[2,3-*d*]pyrimidines and thieno[3,2-*d*]pyrimidines, which should complement existing methods.

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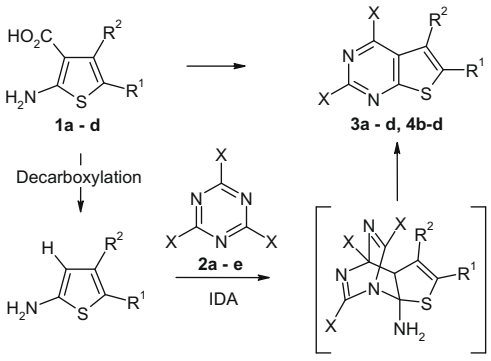
Inverse electron-demand Diels–Alder (IDA) reactions have been developed as a powerful method to construct various heterocycles efficiently.[1] In particular, the IDA reactions with 1,3,5-triazines as azadienes have been applied to the efficient synthesis of pyrimidine derivatives.[2–4] Recently, five-membered heterocycles were introduced as electron-rich dienophiles, and their IDA reactions with 1,3,5-triazines were reported as a one-step synthesis of various pyrimidine-fused heterocycles.[5–8] One common property of electron-rich five-membered heterocycles (e.g., with an amino group as a substituent) is poor thermal stability, which often renders these compounds (such as 5-aminoimidazoles and 2-aminopyrroles) too unstable for isolation. One way to circumvent this issue is to generate these electron-rich dienophiles in situ. In fact, such tandem decarboxylation-IDA reactions using 5-amino-4-imidazolecarboxylic acids and 5-amino-4-pyrazolecarboxylic acids as latent dienophiles[6,8] have been reported. A logical extension of the tandem decarboxylation IDA reaction is to explore the readily available 2-amino-3-thiophenecarboxylic acids, which have been reported to undergo decarboxylation.[9,10] Such new IDA reactions (Scheme 1) could provide an efficient method for the synthesis of thienopyrimidines, which would be complementary to existing methods for rapid synthesis of this class of biologically interesting heterocycles.[11–13]

Various 2-amino-3-thiophenecarboxylic acids were prepared from their corresponding esters via saponification. Initially, 2-amino-4,5,6,7-tetrahydro-benzo[*b*]thiophene-3-carboxylic acid (**1a**) was tested with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (**2a**) under mild thermal conditions, and indeed the desired thieno[2,3-*d*]pyrimidine **3a** was obtained in moderate yield (Table 1, entry 1). The regiochemistry of **3a** was assigned based on 1D Roesy experiments: there is a strong NOE interaction between the $-CH_2-$ at the 3-position of the thiophene moiety and one of the ethyl ester groups. Conversely, if the IDA product is the other regio-isomer thieno[3,2-*d*]pyrimidine (e.g., compound **6**, Eq. 3) then there




**Scheme 1.** IDA reactions of 2-aminothiophenes (**1a–d**).

**Table 1**
IDA reactions of thiophene **1a** with triazines **2a–e**[a]

| Entry | Dienes | X | Conditions | Pdt | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **2a** | $CO_2Et$ | 90 °C, 18 h[c] | **3a** | 20 |
| 2 | **2a** | $CO_2Et$ | 80 °C, 18 h | **3a** | 76 |
| 3 | **2b** | $CF_3$ | 80 °C, 18 h | **3b** | 76 |
| 4 | **2c** | $CF_2Cl$ | 80 °C, 18 h | **3c** | 51 |
| 5 | **2d** | H | 80 °C, 18 h | **3d** | 33 |
| 6 | **2e** | Ph | 80 °C, 18 h | **3e** | 0 |

[a] All reactions were conducted under nitrogen in DMF–AcOH unless otherwise noted.
[b] Yields were based on isolated pure products.
[c] DMSO was used as the solvent.

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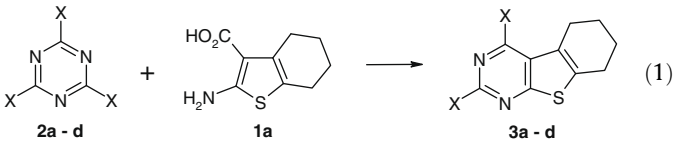
should not be any NOE interaction between the $-CH_2-$ at the 3-position of the thiophene moiety and one of the ethyl ester groups on the pyrimidine side.

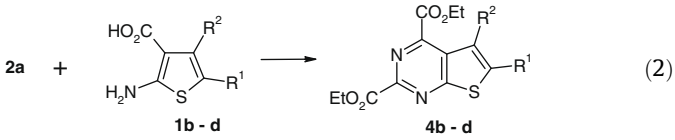
Screening of reaction conditions such as solvent and reaction temperature led to the identification of DMF–AcOH as an optimum solvent system, producing compound **3a** in good yield (76%; entry 2, Table 1). The scope of this tandem decarboxylation IDA reaction was explored using various 1,3,5-triazines (**2a–e**) as the azadienes and thiophene **1a** as the latent dienophile (Eq. 1); results are summarized in Table 1.[18]




(1)

Consistent with past observations, 1,3,5-triazines with electron-withdrawing groups such as ethoxycarbonyl and $CF_3$ gave a higher yield of the desired IDA product (entries 2 and 3) compared to the unsubstituted 1,3,5-triazine (**2d**, entry 5). The 2,4,6-triphenyl-1,3,5-triazine (**2e**) was not reactive enough to participate in the IDA reaction despite prolonged heating (entry 6).

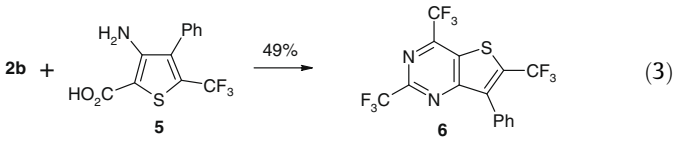
To explore the scope of this IDA reaction with regard to 2-amino-3-thiophenecarboxylic acids, three other thiophenes (**1b–d**) were tested under the current reaction conditions (Eq. 2) and results are summarized in Table 2.




(2)

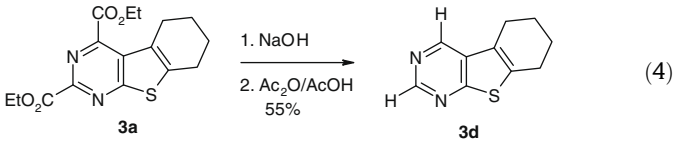
All three 2-amino-3-thiophenecarboxylic acids (**1b–d**) produced the desired IDA products (**4b–d**) in good yields. Both methyl and phenyl substituents are tolerated at the 4- and 5-positions.

Certain 3-amino-2-thiophenecarboxylic acids have been reported to undergo decarboxylation reactions to generate 3-aminothiophenes.[14,15] Theoretical studies[16] suggested that 3-aminothiophenes could also function as dienophiles and would produce the corresponding regioisomer.




(3)

Thus, thiophene **5** was reacted with 1,3,5-triazine **2b** under the preferred reaction conditions and the desired IDA product **6** was obtained in good yield (Eq. 3).




(4)

**Table 2**
IDA reactions of **2a** with thiophenes (**1b-d**)[a]

| Entry | Thiophenes | $R^1$ | $R^2$ | Pdt | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **1b** | Me | Me | **4b** | 47 |
| 2 | **1c** | Ph | H | **4c** | 46 |
| 3 | **1d** | Me | H | **4d** | 55 |

[a] All reactions were conducted under nitrogen in DMF–AcOH unless otherwise noted.
[b] Yields were based on isolated pure products.

Further modification of the IDA products obtained from 1,3,5-triazine **2a** is anticipated to provide access to a wide variety of substituted thienopyrimidines. The activating ester groups may be removed by hydrolysis and decarboxylation to afford compound **3d** (Eq. 4, 55% yield). Alternatively, the two ester groups could be selectively functionalized as Boger et al. reported in their bleomycin work[17] or they could be converted to carboxamides via the corresponding carboxylic acids.

In summary, a series of 2-amino-3-thiophenecarboxylic acids (**1a–d**) and a 3-amino-2-thiophenecarboxylic acid (**5**) were introduced as productive dienophiles in IDA reactions with various 1,3,5-triazines (**2a–e**). This method is useful for the one-step synthesis of both thieno[2,3-*d*]pyrimidines and thieno[3,2-*d*]pyrimidines, which should complement existing methods.

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17. Boger, D. L.; Honda, T.; Dang, Q. *J. Am. Chem. Soc.* **1994**, *116*, 5619–5630.
18. *Representative procedure for the tandem decarboxylation IDA reactions*: A mixture of **1a** (133 mg, 0.672 mmol) and **2a** (100 mg, 0.336 mmol) in anhydrous DMF (3 mL) and acetic acid (0.4 mL) was heated to 80 °C under nitrogen. After 18 h, the cooled reaction solution was evaporated to dryness and the residue was partitioned between EtOAc (50 mL) and saturated sodium bicarbonate (25 mL). The layers were separated and the organic layer was washed (brine, 25 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash chromatography ($SiO_2$, 2 × 15 cm, 20% EtOAc–hexane) to give 5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidine-2,4-dicarboxylate diethyl ester (**3a**) as a light brown solid (85 mg, 76%). mp 52–54 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 4.50 (q, $J$ = 7 Hz, 2H), 4.41 (q, $J$ = 7 Hz, 2H), 2.99 (t, $J$ = 6 Hz, 2H), 2.66 (t, $J$ = 6 Hz, 2H), 1.89–1.83 (m, 4H), 1.38 (t, $J$ = 7 Hz, 3H), 1.37 (t, $J$ = 7 Hz, 3H). MS calcd for $C_{16}H_{18}N_2O_4S$ + $H^+$: 335.4, found 335.4. Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38. Found: C, 57.52; H, 5.30; N, 8.47.
2,4-Bis(trifluoromethyl)-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidine (**3b**) (87 mg, 76%). $^1$H NMR ($CDCl_3$): $\delta$ 3.12-2.82 (m, 4H), 2.06–1.86 (m, 4H). MS calcd for $C_{12}H_8F_6N_2S$+$H^+$: 327.3, found 327.4. Anal. Calcd for $C_{12}H_8F_6N_2S$: C, 44.18; H, 2.47; N, 8.59. Found: C, 44.23; H, 2.48; N, 8.34.
2,4-Bis(chlorodifluoromethyl)-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*] pyrimidine (**3c**) (220 mg, 51.2%). $^1$H NMR ($CDCl_3$): $\delta$ 3.02 (appar. d, $J$ = 6.3 Hz, 4H), 1.95 (appar. dd, $J$ = 2.7, 1.2 Hz, 4H). MS calcd for $C_{12}H_8ClF4N_2S$+$H^+$: 359.0, found 359.1. Anal. Calcd for $C_{12}H_8ClF4N_2S$ + 0.5 $H_2O$: C, 39.15; H, 2.46; N, 7.61. Found: C, 39.11; H, 2.19; N, 7.27.
5,6,7,8-Tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidine (**3d**) (153 mg, 91% pure @254 nM, 32.6%). $^1$H NMR ($CDCl_3$): $\delta$ 7.58 (s, $J$ = 1H), 6.13 (s, 1H), 2.62 (t, $J$ = 5.7 Hz, 2H), 2.48 (t, $J$ = 5.7 Hz, 2H), 1.85–1.81 (m, 4H). MS calcd for $C_{10}H_{10}N_2S$+$H^+$: 191.27, found 191.4.
5,6-Dimethyl-thieno[2,3-*d*]pyrimidine-2,4-dicarboxylate diethyl ester (**4b**) as a foam (419 mg, 47%). $^1$H NMR ($CDCl_3$): $\delta$ 4.57 (q, $J$ = 7.2 Hz, 2H), 4.55 (q, $J$ = 6.9 Hz, 2H), 2.60 (s, 3H), 2.32 (s, 3H), 1.51–1.44 (m, 6H). MS calcd for $C_{14}H_{16}N_2O_4S$ + $H^+$: 309.36, found 309.4. Anal. Calcd for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N, 9.08. Found: C, 54.19; H, 5.11; N, 9.00.
6-Phenyl-thieno[2,3-*d*]pyrimidine-2,4-dicarboxylate diethyl ester (**4c**) (370 mg, 46%). mp 108–110 °C. $^1$H NMR ($CDCl_3$): $\delta$ 8.33 (s, 1H), 7.84–7.81 (m, 2H), 7.53–7.50 (m, 3H), 4.61 (q, $J$ = 7.2 Hz, 4H), 1.55 (t, $J$ = 6.9 Hz, 3H), 1.52 (t, $J$ = 7.2 Hz, 3H). MS calcd for $C_{18}H_{16}N_2O_4S$ + $H^+$: 357.4, found 357.4. Anal. Calcd for $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.52; N, 7.86. Found: C, 60.89; H, 4.75; N, 7.71.
6-Methyl-thieno[2,3-*d*]pyrimidine-2,4-dicarboxylate diethyl ester (**4d**) (519 mg, 55%). mp 95–97 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.78 (s, 1H), 4.61–4.53 (m, 4H), 2.74 (s, 3H), 1.53–1.47 (m, 6H). MS calcd for $C_{13}H_{14}N_2O_4S$ + $H^+$: 295.3,

found 295.1. Anal. Calcd for $C_{13}H_{14}N_2O_4S + 0.2\ H_2O$: C, 52.41; H, 4.87; N, 9.40. Found: C, 52.07; H, 4.98; N, 9.60.

7-Phenyl-2,4,6-tris-trifluoromethyl-thieno[3,2-*d*]pyrimidine (**6**) (71 mg, 49%). $^1$H NMR (DMSO-$d_6$): $\delta$ 7.62–7.61 (m, 3H), 4.41 (q, $J$ = 7 Hz, 2H). MS calcd for $C_{15}H_5N_2S + H^+$: 417.27, found 417.4. Anal. Calcd for $C_{15}H_5N_2F_9S + 0.2\ C_6H_{14}$: C, 44.88; H, 1.81; N, 6.46. Found: C, 44.76; H, 1.66; N, 6.43.