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An efficient entry to furo[2,3-*d*]pyrimidines via inverse electron demand Diels–Alder reactions of 2-aminofurans with 1,3,5-triazines

Qun Dang *, Yan Liu

Department of Chemistry, Metabasis Therapeutics, Inc., 11119 North Torrey Pines Road, La Jolla, CA 92037, USA

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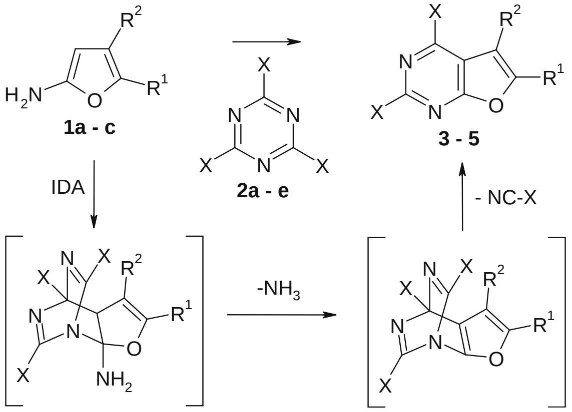
ABSTRACT

Furo[2,3-*d*]pyrimidines were readily prepared via an inverse electron demand Diels–Alder (IDA) reaction between 2-aminofurans and 1,3,5-triazines. 2-Aminofurans proved to be productive dienophiles leading to the IDA product in moderate to good yields. This study further expanded the scope of 1,3,5-triazine IDA reactions with five-membered aromatic heterocycles as dienophiles.

Furo[2,3-*d*]pyrimidines are an interesting class of heterocycles with various biological activities. For example, furo[2,3-*d*]pyrimidines were reported to be potent and selective glycogen synthase kinase-3 inhibitors[1] and antifolate agents.[2] Furo[2,3-*d*]pyrimidines are often prepared via stepwise cyclization reactions.[3,4] A potential alternative method to prepare furo[2,3-*d*]pyrimidines was envisioned to entail cascade reactions involving an inverse electron demand Diels–Alder (IDA) reaction, followed by the elimination of ammonia, and a final retro Diels–Alder reaction, depicted in Scheme 1.

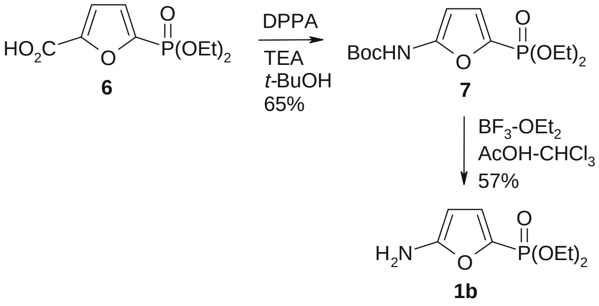


Scheme 1. IDA reactions of 2-aminofurans with triazines.

Furans are often reported as dienes for Diels–Alder reactions,[5–9] but less frequently as dienophiles.[10–12] For example, the Padwa group demonstrated 2-aminofurans as productive dienes for Diels–Alder reactions and developed these reactions into elegant methods to prepare substituted anilines efficiently.[13] To date, 1,3,5-triazine IDA reactions involving furans have not been reported. Herein the investigation of 2-aminofurans as dienophiles in IDA reactions of 1,3,5-triazines and the development of this method for the efficient preparation of furo[2,3-*d*]pyrimidines is reported. Such a method should produce highly substituted furo[2,3-*d*]pyrimidines and complement existing methods to access this interesting class of heterocycles.

The 2-*N*-Boc-amino-furan **7** was readily prepared from 2-furoic acid **6** via a Curtius rearrangement[14] as shown in Scheme 2.

Treatment of 2-furoic acid **6** with diphenyl phosphorylazide (DPPA) and triethylamine (TEA) in refluxing *tert*-butanol gave the Boc-protected 2-aminofuran **7** in 65% yield. Removal of the Boc group proved to be more complicated since several conventional methods did not produce the desired 2-aminofuran **1b**. Thus, treatment of furan **7** with TFA (10 equiv) in anhydrous CH_2Cl_2 at 25 °C for 18 h led to mostly decomposition, while milder conditions such as TMSCl (5 equiv) in EtOH, 25 °C, 24 h, and *p*TsOH (0.1 equiv) in refluxing toluene (110 °C), 24 h led to mostly starting furan **7** being recovered. Conversely, the Lewis acid BF_3–OEt_2 promoted Boc re-



Scheme 2. Syntheses of 2-aminofurans **7** and **1b**.

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* Corresponding author at present address: Merck Research Laboratories, Rahway, NJ 07065, USA. Tel.: +1 732 594 2018; fax: +1 732 594 7444.
E-mail address: qun_dang@merck.com (Q. Dang).

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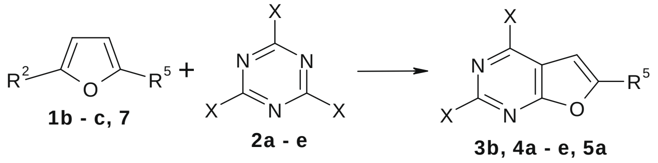
moval method developed by Hiskey et al.[15] generated the desired 2-aminofuran **1b** in 57% yield (unoptimized).

The IDA reactions with 1,3,5-triazines (**2a–e**) were investigated using furans **7, 1a** (methyl 2-amino-5-furancarboxylate), **1b** and **1c** (2-methoxy-furan); results are summarized in Table 1.[16]

Although 2-aminofurans were reported as the 4π diene in Diels–Alder reactions by Padwa and co-workers, no example of 2-aminofurans as dienophiles was uncovered. Initially, IDA reactions were investigated using 2-aminofuran **1a** and 2 equiv of triazine **2b** (which was chosen based on better solubility compared to triazine **2a**). After 24 h at room temperature, most of **1a** were consumed but several products were detected by TLC, which are likely products associated with the various stages of this cascade reaction (Scheme 1). Heating of the reaction solution at 80 °C for 12 h generated a single product, which was isolated and identified as the desired IDA product **3b** in 75% yield, Table 1, entry 1. Conducting the reaction at 80 °C for 18 h gave a slightly lower yield of 64% (Table 1, entry 2), while heating at 100 °C for 12 h gave compound **3b** in 75% yield (Table 1, entry 3). Furan **1b** also proved to be a productive dienophile in the IDA reaction with triazines **2b** and **2a** under thermal conditions, leading to **4b** and **4a** in 63% and 52% yields, respectively (Table 1, entries 4 and 5). Encouraged by these results, the Boc-protected 2-aminofuran **7** was also investigated as a potential dienophile. However, after prolonged heating of furan **7** and triazine **2b** at 100 °C for 24 h, no IDA product **4b** was detected; only starting materials remained. The significantly decreased reactivity of furan **7** compared to furan **1b** in the current IDA reactions is likely due to the electron-withdrawing ability of the Boc group. Thus, various conditions were explored to combine the Boc removal and IDA reaction into a one-pot procedure. Furan **7** was treated with triazine **2a** under the Hiskey Boc deprotection conditions (4 equiv BF_3–OEt_2, AcOH–$CHCl_3$, 25 °C, 15 h) and indeed the desired IDA product **4a** was isolated in 50% yield (Table 1, entry 7). To test the importance of the Lewis acid BF_3–OEt_2, the reaction was run with a lower amount or no BF_3–OEt_2: 2 equiv of BF_3–OEt_2 led to a lower yield (Table 1, entry 8), while eliminating BF_3–OEt_2 did not produce any desired product (Table 1, entries 9 and 10). These observations suggest that BF_3–OEt_2 is essential for this one-pot procedure, while the AcOH–$CHCl_3$ solvent system alone is not enough to promote the one-pot procedure. Alternatively, an ionic liquid (1-butyl-3-methylimidazolium tetrafluoroborate) was found to be suitable for the one-pot Boc removal IDA reaction and with the same efficiency in generating the IDA product **4a** (Table 1, entry 11). Next, furan **7** was reacted with triazines **2b**–**e** under the newly developed Lewis acid-promoted IDA reaction conditions. Triazines **2a** and **2b** (with electron-withdrawing groups such as ethoxycarbonyl and CF_3) gave higher yields of the desired IDA products (entries 7 and 12) compared to the unsubstituted triazine **2c** (entry 13). Omitting acetic acid from the reaction of triazine **2c** and furan **1b** gave comparable yield of the IDA product **4c** (entry 14), while conducting the reaction in neat BF_3–OEt_2 significantly increased the yield of **4c** from 30% to 57% (entry 15). It is noteworthy that even though the IDA reaction of furan **1b** with triethyl triazine **2d** only gave **4d** in moderate yield (entry 16), this is the first example of triazine **2d** participating in an IDA reaction. The more electron-rich triazine **2e** was not reactive enough for the current IDA reaction (entry 17). To check if the Lewis acid reaction conditions are compatible with other 2-aminofurans, furan **1a** was reacted with triazine **2b** in the presence of BF_3–OEt_2, but much lower yield of **3b** was obtained (entry 18) compared to the conventional thermal conditions (entry 3). Another furan derivative shown to participate in IDA reactions is 2-methoxyfuran (**1c**); Liao et al. reported reactions of furan **1c** with electron-deficient pyrones under thermal conditions.[12] Treatment of triazine **2a** with furan **1c** under either thermal conditions (starting materials remained, entry 19) or Lewis acid conditions (decompositions observed, entry 20) did not produce any desired IDA products. Thus, furan **1c** is not reactive enough for an IDA reaction with triazine **2a**, which is

Table 1

IDA reactions of furans with various 1,3,5-triazines leading to furo[2,3-*d*]pyrimidines[a]



Entry	R^2	R^5	Furans	X	Triazines	Conditions	Pdt	Yield (%)
1	H_2N	CO_2Me	**1a**	CF_3	**2b**	DMSO, 25 °C, 24 h; 80 °C, 12 h	**3b**	75
2	H_2N	CO_2Me	**1a**	CF_3	**2b**	DMSO, 80 °C, 18 h	**3b**	64
3	H_2N	CO_2Me	**1a**	CF_3	**2b**	DMSO, 100 °C, 18 h	**3b**	75
4	H_2N	$PO(OEt)_2$	**1b**	CF_3	**2b**	DMF, 100 °C, 18 h	**4b**	63
5	H_2N	$PO(OEt)_2$	**1b**	CO_2Et	**2a**	DMSO–DMF (1:1), 100 °C, 18 h	**4a**	52
6	BocHN	$PO(OEt)_2$	**7**	CF_3	**2b**	DMSO, 100 °C, 24 h	**4a**	0[b]
7	BocHN	$PO(OEt)_2$	**7**	CO_2Et	**2a**	BF_3–OEt_2 (4 equiv), AcOH–$CHCl_3$, 25 °C, 15 h	**4a**	50[c]
8	BocHN	$PO(OEt)_2$	**7**	CO_2Et	**2a**	BF_3–OEt_2 (2 equiv), AcOH–$CHCl_3$, 25 °C, 15 h	**4a**	36
9	BocHN	$PO(OEt)_2$	**7**	CO_2Et	**2a**	AcOH–$CHCl_3$, 25 °C, 24 h	**4a**	0[b]
10	BocHN	$PO(OEt)_2$	**7**	CO_2Et	**2a**	AcOH–DMF, 100 °C, 48 h	**4a**	0[b]
11	BocHN	$PO(OEt)_2$	**7**	CO_2Et	**2a**	BF_3–OEt_2 (4 equiv), ionic liquid,[d] 25 °C, 15 h	**4a**	52[c]
12	BocHN	$PO(OEt)_2$	**7**	CF_3	**2b**	BF_3–OEt_2 (4 equiv), AcOH–$CHCl_3$, 25 °C, 15 h	**4b**	68[c]
13	BocHN	$PO(OEt)_2$	**7**	H	**2c**	BF_3–OEt_2 (4 equiv), AcOH–$CHCl_3$, 25 °C, 15 h	**4c**	33[c]
14	BocHN	$PO(OEt)_2$	**7**	H	**2c**	BF_3–OEt_2 (4 equiv), $CHCl_3$, 25 °C, 15 h	**4c**	30[c]
15	BocHN	$PO(OEt)_2$	**7**	H	**2c**	BF_3–OEt_2 (35 equiv), 25 °C, 15 h	**4c**	57[c]
16	BocHN	$PO(OEt)_2$	**7**	Et	**2d**	BF_3–OEt_2 (35 equiv), 25 °C, 15 h	**4d**	28[c]
17	BocHN	$PO(OEt)_2$	**7**	OMe	**2e**	BF_3–OEt_2 (4 equiv), AcOH–$CHCl_3$, 25 °C, 15 h	**4e**	0[c]
18	H_2N	CO_2Me	**1a**	CF_3	**2b**	BF_3–OEt_2 (4 equiv), AcOH–$CHCl_3$, 25 °C, 15 h	**3b**	27
19	MeO	H	**1c**	CO_2Et	**2a**	DMSO, 100 °C, 24 h	**5a**	0[b]
20	MeO	H	**1c**	CO_2Et	**2a**	BF_3–OEt_2 (4 equiv), AcOH–$CHCl_3$, 25 °C, 15 h	**5a**	0

[a] All reactions were conducted under nitrogen and yields are based on isolated products.

[b] Starting materials remained.

[c] Furan **7** was consumed.

[d] 1-Butyl-3-methylimidazolium tetrafluoroborate.

likely due to the relatively weaker electron-donating property of a methoxy group compared to an amino group.

In summary, 2-amino-furans **1a** and **1b** were introduced as productive dienophiles in IDA reactions with various 1,3,5-triazines (**2a**–**e**), leading to furo[2,3-*d*]pyrimidines in moderate to good yields. A one-pot Boc removal and IDA reaction procedure was also developed to allow the otherwise unreactive *N*-Boc 2-amino-furan **7** to productively participate in the IDA reaction with various 1,3,5-triazines. Moreover, a Lewis acid, BF_3–OEt_2, was shown for the first time to be compatible with triazine IDA reactions, and able to improve yields for 1,3,5-triazines **2c** and **2d**, which were often reported to have lower reactivity compared to the more electron-deficient 1,3,5-triazines **2a** and **2b**.

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16. *Representative procedures for the IDA reactions:* A mixture of **2b** (312 mg, 1.10 mmol) and **1b** (120 mg, 0.55 mmol) in anhydrous DMSO (2 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, 30% EtOAc–hexane) to give 6-diethylphosphono-2,4-bis(trifluoromethyl)-furo[2,3-*d*]pyrimidine (**4b**) as a light oil (136 mg, 63%). Alternatively, compound **4b** was prepared using the one-pot Lewis acid-promoted Boc deprotection and IDA reaction: A mixture of **2b** (114 mg, 0.40 mmol) and **7** (64 mg, 0.2 mmol) in anhydrous $CHCl_3$–AcOH (5:1, 1 mL) was treated with BF_3–OEt_2 (0.8 mmol) at 25 °C under nitrogen. After 15 h, the reaction solution was quenched with dilute sodium hydroxide (0.1 N, 20 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash chromatography (SiO_2, 1 × 15 cm, 30% EtOAc–hexane) to give 6-diethyl-phosphono-2,4-bis(trifluoromethyl)-furo[2,3-*d*]pyrimidine (**4b**) as a light oil (53 mg, 68%).^{1}H NMR (DMSO-d_6): δ 7.17 (m, 1H), 4.31 (m, 4H), 1.31 (m, 6H). MS calcd for $C_{12}H_{11}N_2O_4PF_6 + H^+$: 393.3, found 393.3. Anal. Calcd for $C_{12}H_{11}N_2O_4PF_6$: C, 36.75; H, 2.83; N, 7.14. Found: C, 36.71; H, 2.61; N, 7.39.