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Efficient Synthesis of Pyrimido[1,2-*c*][1,3]benzothiazin-6-imines and Related Tricyclic Heterocycles by S_NAr-Type C−S, C−N, or C−O Bond Formation with Heterocumulenes

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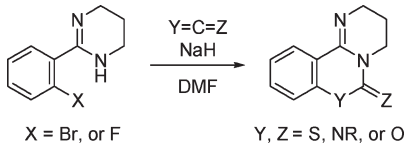

A simple and practical synthetic method of pyrimido[1,2-*c*]-[1,3]benzothiazin-6-imines and related tricyclic heterocycles has been developed. Treatment of 2-(2-haloaryl)-tetrahydropyrimidines with NaH and a heterocumulene such as carbon disulfide, isothiocyanates, and isocyanates in DMF provides the desired cyclization products through a regioselective S_NAr-type reaction. This method provides direct access to PD 404182 and related compounds.

The pyrimidobenzothiazine derivative PD 404182 (**1**) was recently discovered to be an antibiotic agent (Figure 1).[1,2]

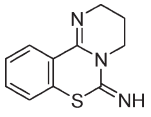

FIGURE 1. Structure of PD 404182.

This compound inhibits 3-deoxy-D-*manno*-octulosonic acid 8-phosphate (KDO 8-P) synthase, which catalyzes the condensation of phosphoenolpyruvate and arabinose 5-phosphate in the first committed step in the synthesis of KDO (an integral part of the lipopolysaccharide layer in Gram-negative bacteria). PD 404182 is considered to be an important lead in the development of structurally novel antibiotics effective against multidrug-resistant bacteria.[2b] Extensive study of the structure−activity relationship (SAR) of PD 404182 has not been carried out, presumably due to the lack of an efficient synthetic method suitable for lead optimization, as well as the cost of commercially available PD 404182.[3]

To develop a reliable, short-step synthetic method of tricyclic heterocycles related to PD 404182, we planned a novel strategy based on carbon (sp^2)−heteroatom bond formation using 2-(2-haloaryl)tetrahydropyrimidine derivatives. The carbon−heteroatom bond formation reaction is becoming a powerful methodology for construction of various heterocycles, providing several biologically active compounds.[4] The nucleophilic aromatic substitution (S_NAr) reaction is a well-established transition metal-free[5,6] carbon−heteroatom bond formation reaction.[7,8] In general, the S_NAr reaction requires harsh conditions (>100 °C) and/or sufficiently activated aromatic rings by powerful electron-withdrawing group(s) (e.g., nitro). We describe a direct synthesis of tricyclic heterocycles related to PD 404182 by a regioselective S_NAr-type reaction of tetrahydropyrimidine-substituted haloarenes with heterocumulene in the absence of additional electron-withdrawing groups.[9] The efficient short-step synthesis of PD 404182 is also presented.

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(3) $76.20/2 mg, Sigma-Aldrich.

(4) For reviews on transition metal-catalyzed carbon−heteroatom bond formation, see: (a) Hartwig, J. F. *Synlett* **1997**, 329–340. (b) Baranano, G. M.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287–305. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067. (d) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860. (e) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818. (f) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417–1423. (g) Yang, B. Y.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146. (h) Hassan, J.; Sevingnon, M.; Gozzi, C.; Shulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469. (i) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209. (j) Littke, A. F.; Fu, C. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4177–4211. (k) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.

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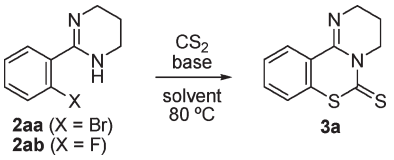
TABLE 1. Optimization of Reaction Conditions with CS_2[a]



entry	X	base (equiv)	solvent	time (h)	yield (%)[b]
1	Br	NaH (5)	MeCN	4	trace
2	Br	NaH (5)	THF	4	trace
3	Br	NaH (5)	DMF	6	75
4	Br	NaH (2)	DMF	12	88
5	Br	none	DMF	12	12
6	Br	Et_3N (2)	DMF	12	trace
7	Br	KH (2)	DMF	6	trace
8	Br	NaO*t*-Bu (2)	DMF	6	27
9	F	NaH (2)	DMF	12	86

[a]All reactions were carried out at 80 °C with 2 or 5 equiv of CS_2 (corresponding to the base loading). [b]Isolated yields.

Initial experiments were carried out with bromoarene **2aa**, which can be readily obtained by oxidative amidination[10] of 2-bromobenzaldehyde with propanediamine, and carbon disulfide as a heterocumulene (Table 1). Exposure of **2aa** with sodium hydride (5.0 equiv) and carbon disulfide (5.0 equiv) in acetonitrile or THF afforded only a trace amount of desired compound **3a** (entries 1 and 2). The desired reaction was efficiently promoted in DMF to give **3a** in 75% yield (entry 3). A decreasing amount of sodium hydride and carbon disulfide (2.0 equiv) slightly improved the yield of **3a** (88%) under the reaction for 12 h (entry 4).[11] The reaction in the absence of sodium hydride provided a yield of **3a** of only 12%. We next screened several bases such as triethylamine, potassium hydride[12] and sodium *tert*-butoxide (entries 6−8): sodium hydride was the most effective (entry 4). The fluoride **2ab** gave a comparable result with the bromide **2aa** to afford **3a** in 86% yield under optimized conditions (entry 9).

With knowledge of the optimized conditions, we examined the reaction of several substituted substrates (Table 2). Substrates **2b**−**d** having a methoxy, methyl, or fluoro group at the 4-position provided the corresponding cyclized products **3b**−**d** in good-to-excellent yields (76−95%, entries 1−3). Whereas the reaction of **2e** bearing the 4-nitro group at 80 °C resulted in formation of a complex mixture, the reaction at room temperature gave the cyclization product **3e** in 73% yield (entry 4). A methoxy group on the 5-position considerably diminished the reactivity, affording **3f** in only 17% yield (entry 5). This was presumably due to increased electron density at the carbon substituted by a bromine atom. In the case of **2g** bearing a 5-nitro group, the corresponding product **3g** was obtained by the reaction at room temperature (entry 6), similarly to **2e** (entry 4). Pyridine derivatives **4** and **6** showed different reactivity depending on the position of the nitrogen atom: the 2-bromopyridine derivative **6** gave a better result (71%, entry 8) than the 3-bromopyridine derivative **4** (18%, entry 7). The naphthalene derivative **8** afforded the tetracyclic compound **9** in quantitative yield (entry 9).

TABLE 2. Reaction of Substituted 2-(2-Halophenyl)-1,4,5,6-tetrahydropyrimidines[a]

entry	substrate	product	yield (%)[b]
1	**2b** (R = OMe, X = F)	**3b** (R = OMe)	95
2	**2c** (R = Me, X = Br)	**3c** (R = Me)	88
3	**2d** (R = F, X = Br)	**3d** (R = F)	76
4	**2e** (R = NO_2, X = F)	**3e** (R = NO_2)	–[c] (73)[d]
5	**2f** (R = OMe)	**3f** (R = OMe)	17
6	**2g** (R = NO_2)	**3g** (R = NO_2)	–[c] (57)[d]
7	**4**	**5**	18
8	**6**	**7**	71
9	**8**	**9**	quant.

[a]Unless otherwise stated, reactions were carried out with CS_2 (2.0 equiv) and NaH (2.0 equiv) in DMF at 80 °C for 12 h. [b]Isolated yields. [c]A complex mixture formed. [d]Yields in parentheses indicate those of the reactions at rt.

To further expand our methodology for construction of other heterocyclic frameworks, we investigated the reaction using isothiocyanates or isocyanates[13,14] as heterocumulene (Table 3). When benzylisothiocyanate was employed, the reaction of **2aa** or **2ab** efficiently proceeded to give the corresponding *N*-arylated product **10** in 82% and 97% yields, respectively (entries 1 and 2). The reaction with *tert*-butylisothiocyanate exclusively furnished an *S*-arylated product **11** as a single isomer (entry 3). These results indicate

(10) Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474–1480.
(11) Larger amounts of unidentified byproduct were formed when using 5 equiv of NaH than in the reaction with 2 equiv of NaH (entry 4).
(12) A reason for the significant countercation effect (NaH vs. KH) on the reactivity is unclear.
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TABLE 3. Reaction with Isothiocyanates or Isocyanates[a]

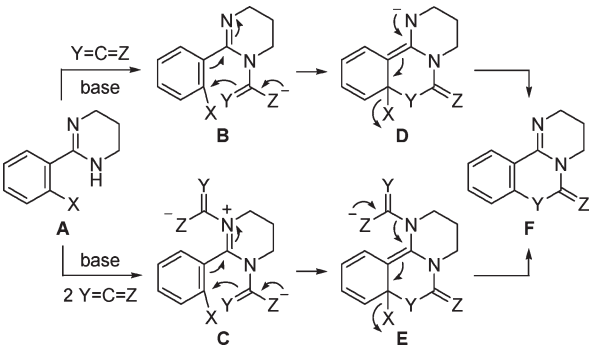
entry	substrate	R-NCX	product	yield (%)[b]
1	**2aa** (X = Br)	BnNCS	**10**	82
2	**2ab** (X = F)			97
3[c]	**2ab**	*t*-BuNCS	**11**	62[d,e]
4	**2ab**	BnNCO	**12**	quant.
5[c]	**2ab**	*t*-BuNCO	**13** (Y = N*t*-Bu, Z = O)	54
			14 (Y = O, Z = N*t*-Bu)	18[e]
6	**2ab**	PhNCO	**15**	quant.
7	**16**	*t*-BuNCS	**17**	49[e]

[a]Unless otherwise stated, reactions were carried out with R-NCX (2.0 equiv) and NaH (2.0 equiv) in DMF at rt for 2−3 h. [b]Isolated yields. [c]These reactions were carried out at 80 °C. [d]A trace amount of regioisomeric *N*-arylation product was also formed. [e]Isolated as a single isomer.

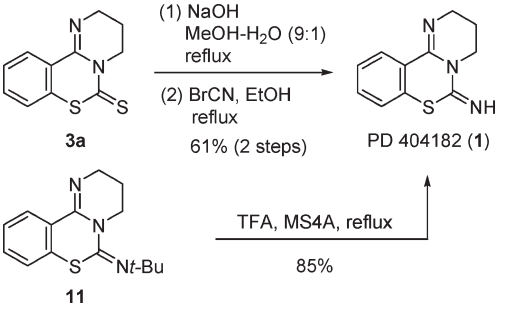
that the regioselectivity of the reaction can be perfectly switched by changing a substituent on the nitrogen atom. As expected, the reaction of **2ab** with benzylisocyanate provided an *N*-arylated product **12** in quantitative yield (entry 4) as in the case with isothiocyanate (entries 1 and 2). Interestingly, *tert*-butylisocyanate showed moderate selectivity to mainly afford an *N*-arylation product **13** (54%), formed by the arylation at the more bulky position, as well as an *O*-arylation product **14** (18%, entry 5). Phenylisocyanate also provided an *N*-arylated product **15** (entry 6). The 2-phenylimidazoline derivative **16** (a 5-membered-ring amidine congener) also provided the corresponding *S*-arylated product **17** in a slightly decreased yield (49%, entry 7).

This reaction would proceed via nucleophilic addition of the amidine moiety to heterocumulene followed by an intramolecular S_NAr reaction of the resulting adducts such as **B** (Scheme 1). Nonactivated aromatic rings efficiently reacted under relatively mild conditions, so two molecules of

SCHEME 1. Proposed Reaction Mechanisms



SCHEME 2. Synthesis of PD 404182



the heterocumulene may be involved in the reaction to form the intermediate **C** in which the amidine moiety can be a more powerful electron-withdrawing group suitable for the S_NAr-type reaction. The regioselectivity in the nucleophilic attack on the aromatic ring (Y vs. Z) is controlled by a subtle balance of inherent nucleophilicity and steric hindrance of these functionalities.

We finally focused on the synthesis of PD 404182 (**1**) (Scheme 2). Hydrolysis of the carbamodithioate derivative **3a** followed by treatment with cyanogen bromide[15] readily afforded the desired compound **1**. The same compound was also obtained in a single step by heating compound **11** in trifluoroacetic acid in the presence of molecular sieves.

In conclusion, we developed a simple and practical synthetic method for tricyclic heteroarenes related to PD 404182. This reaction provides divergent access to several related heterocycles under mild conditions without a powerful activating group. Further investigations including SAR study of these derivatives are currently underway.

Experimental Section

General Procedure for Synthesis of 3,4-Dihydro-2*H*-pyrimido-[1,2-*c*][1,3]benzothiazine-6-thione (3a) (Table 1, Entry 4). To a mixture of **2aa** (59.8 mg, 0.25 mmol) and NaH (20.0 mg, 0.50 mmol; 60% oil suspension) in DMF (0.83 mL) was added carbon disulfide (30.5 μL, 0.50 mmol) under an Ar atmosphere. After being stirred at 80 °C for 12 h, the mixture was concentrated in vacuo. The residue was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (9:1) to give compound **3a** as a pale-yellow solid (51.4 mg, 88%): mp 139−141 °C (from $CHCl_3$−*n*-hexane); IR (neat) (cm^{-1}) 1624 (C=N); ^1H NMR (400 MHz, $CDCl_3$) δ 2.01−2.07 (m, 2H,

(15) Peter, S.; Gerhard, S. *Ger. Offen.* DE2811131, 1979.

CH_2), 3.76 (t, J = 5.6 Hz, 2H, CH_2), 4.45 (t, J = 6.2 Hz, 2H, CH_2), 7.03 (dd, J = 7.8, 1.5 Hz, 1H, Ar), 7.28−7.33 (m, 1H, Ar), 7.41 (ddd, J = 8.0, 7.6, 1.5 Hz, 1H, Ar), 8.20 (dd, J = 8.0, 1.2 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 45.5, 48.6, 121.6, 126.5, 127.5, 128.9, 131.1, 131.8, 144.2, 189.8. Anal. Calcd for $C_{11}H_{10}N_2S_2$: C, 56.38; H, 4.30; N, 11.95. Found: C, 56.23; H, 4.44; N, 11.85.

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Supporting Information Available: Experimental procedures, full characterization, and ^{1}H and ^{13}C NMR charts of substrates and cyclization products. This material is available free of charge via the Internet at http://pubs.acs.org.