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6,8-Dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione: a novel method of pyrrole-ring annulation to an azine nucleus based on a tandem S_N^H–S_N^H process

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Abstract—6,8-Dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione has been shown to react with some secondary amines in the presence of an oxidant to produce 6,8-dimethylpyrrolo[2′,3′;3,4]pyridazino[6,5-*d*]pyrimidine-7,9(6*H*,8*H*)-dione derivatives. The reaction represents a new method of pyrrole-ring annulation to an azine nucleus via a tandem S_N^H–S_N^H process.

Recently, we have shown that 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione **1** reacts with ammonia or primary amines in the presence of an oxidant to give the corresponding 4-amino derivatives **2** in good yields (Fig. 1).[1] A similar reaction with secondary amines such as dimethylamine, piperidine or morpholine proceeds with difficulty and leads to 3-amino derivatives **3**, in moderate yields.[1] A remarkable peculiarity of pyridazine **1** is its ability to undergo tandem S_N^H–S_N^H amination with α,ω-diaminoalkanes to produce trinuclear heterocyclic systems such as **4**.[2]

Herein, we wish to describe the unusual and preparatively useful example of the tandem S_N^H–S_N^H reaction of **1** with secondary acyclic amines in which the latter behave as bifunctional *C*,*N*-nucleophiles. It turns out that treatment of **1** with diethylamine in the presence of $AgPy_2MnO_4$ affords, unexpectedly, 6,8-dimethyl-3 - ethylpyrrolo[2′,3′;3,4]pyridazino[6,5 - *d*]pyrimidine-7,9(6*H*,8*H*)-dione **12a** as a single product in 42% yield (Scheme 1). The molecular structure of **12a** was confirmed by IR, ^{1}H and ^{13}C NMR, MS and X-ray structural data obtained for its perchlorate (Fig. 2).[†] The reaction of **1** with di-*n*-propyl-, di-*n*-butyl- or methyl-*n*-propylamine proceeds similarly giving rise to pyrroles **12b–d**.[‡]

Although the mechanism of the above reaction needs to be studied in detail, it seems to occur in accordance with Scheme 1. The process starts from oxidation of the secondary amine **5** into the Schiff base **6**, which reacts further with **1** through the enamine **7**.[§] The heterocyclic-substrate couples with **7**, firstly, via its most electron-deficient atom C-4 (**1**→**8**) and then intramolecularly via the C-3 position (**9**→**10**). Both nucleophilic reactions are accompanied by an oxidative step (**8**→**9**, **11**→**12**). Thus, the whole transformation actually includes two consecutive S_N^H reactions in which the dialkylamino reagent at first behaves as a *C*-nucleophile and then as an *N*-nucleophile. This view is supported by the following experiment. When pyridazine **1** was treated with imines **6a**,**b**,**d**,**e** (prepared from the corresponding aldehydes and primary amines) pyrroles **12a**,**b**,**d**,**e** were isolated in 11–44% yields.

The reactions of other related heterocycles with secondary amines are at present under study. Evidently,

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† The following crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 160133.

‡ Pyrroles **12** display a typical indole-like reactivity. For instance, **12a** can be easily brominated (Br_2–AcOH), nitrated (HNO_3–AcOH), formylated ($POCl_3$–DMF), aminomethylated (CH_2O–piperidine), and hydroxymethylated to yield β-substituted derivatives **13a–e**, respectively.

§ This assumption is in agreement with the earlier observation that diethylamine and triethylamine in the presence of an oxidant are able to generate enamines, which can react further as dienophiles in some [4+2]-cycloaddition reactions.[3,4]

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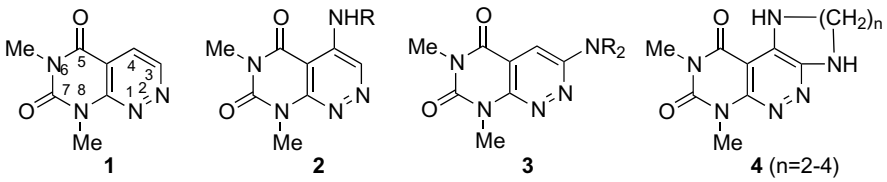
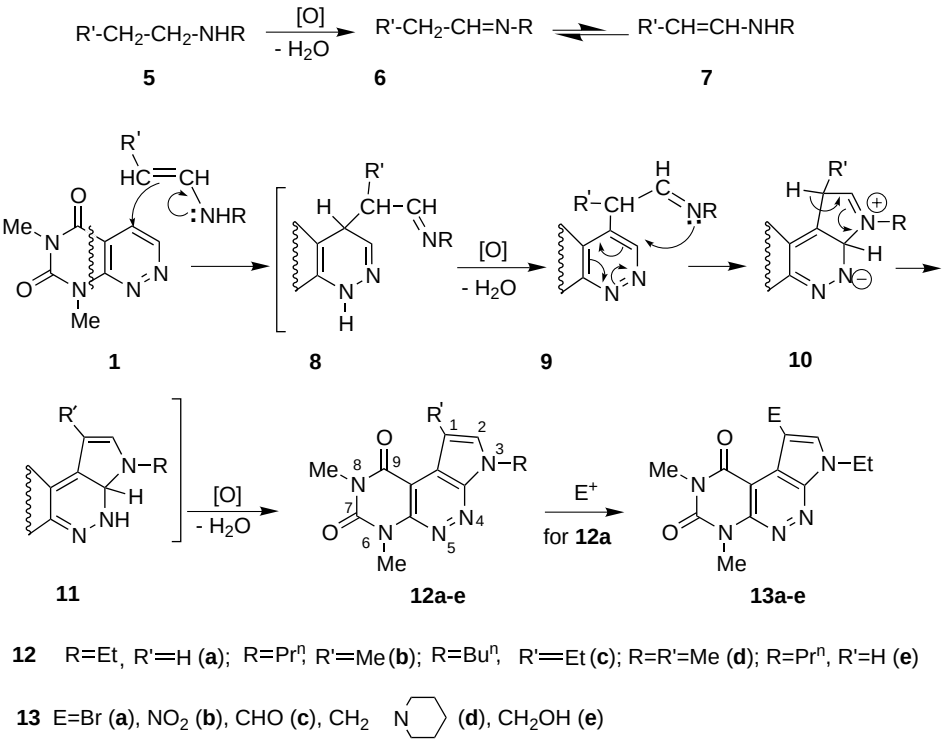


Figure 1.



Scheme 1.

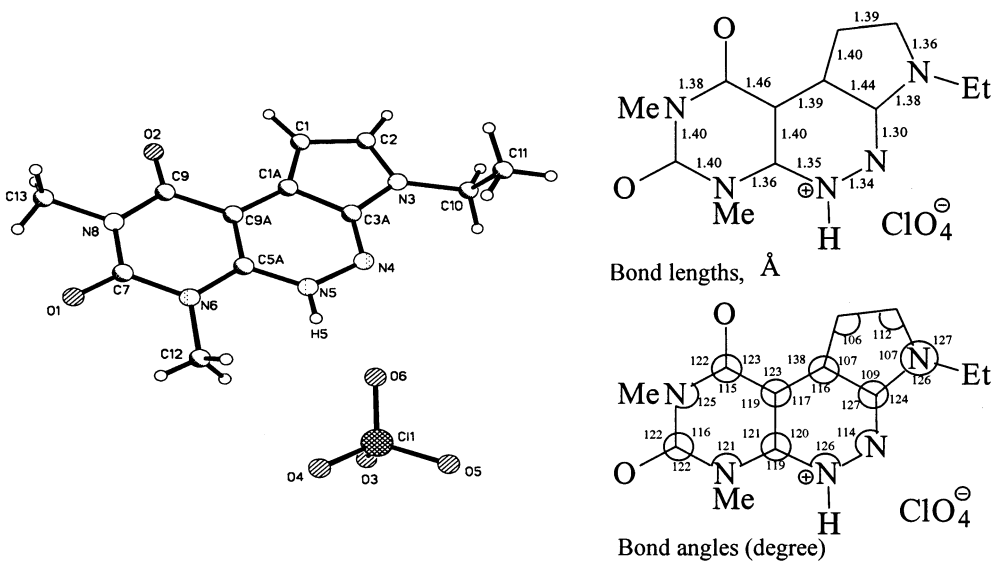


Figure 2. Molecular structure of **12a** perchlorate with crystallographic numbering scheme.

such substrates must have two adjacent electrophilic carbon atoms in the azine ring. There are two main requirements for the dialkylamine to produce pyrroles **12**: (i) its alkyl groups should be flexible and (ii) it must have at least one alkyl chain with two or more carbon atoms.

In summary, we have presented a previously unknown type of pyrrole-ring annulation (cf. Refs. 5 and 6). In addition, the reported reaction represents the first example[7] of a tandem S_N^H–S_N^H process in neutral azines with the participation of a bifunctional *C*,*N*-nucleophile.

Experimental: To a stirred solution of **1** (0.35 g, 1.8 mmol) in diethylamine (30 ml), $AgPy_2MnO_4$ (0.9 g, 2.3 mmol) was added in portions at 15°C. After a week of stirring at 20°C the liquid phase was concentrated to dryness. The residue was extracted with boiling $CHCl_3$ (50 ml). TLC on Al_2O_3 ($CHCl_3$) followed by recrystallization from EtOH gave **12a** (0.2 g, 42%) as yellow crystals.

For **12a**: mp 225–227°C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.58 (t, J=7.3 Hz, 3H, $CH_2\underline{Me}$), 3.52 (s, 3H, 6-Me), 3.96 (s, 3H, 8-Me), 4.56 (q, J=7.3 Hz, 2H, CH_2), 7.23 (d, J=3.2 Hz, 1-H), 7.81 (d, J=3.2 Hz, 2-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.56 (Me), 28.30 (6-Me), 30.40 (8-Me), 40.62 (CH_2), 100.01 (1-C), 102.97, 120.75, 139.05 (2-C), 144.50, 146.59, 150.98 (7-C), 161.88 (9-C); IR (KBr): 1658, 1703 cm^{-1} (C=O); MS (m/z): 259 (M^+).

For **12b**: mp 174–175°C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.93 (t, J=7.3 Hz, 3H, $CH_2CH_2\underline{Me}$), 1.94 (m, 2H, $CH_2\underline{CH_2}Me$), 2.68 (s, 3H, 1-Me), 3.51 (s, 3H, 6-Me), 3.94 (s, 3H, 8-Me), 4.39 (q, J=7.3 Hz, 2H, $\underline{CH_2}CH_2Me$), 7.52 (s, 1H, 2-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.19 (Me), 14.20 (CH_2), 23.54 (1-Me), 28.50 (6-Me), 30.65 (8-Me), 40.86 (CH_2), 104.59, 110.67 (1-C), 119.33, 138.82 (2-C), 146.52, 150.79 (7-C), 151.43, 161.63 (9-C); IR (KBr): 1660, 1706 cm^{-1} (C=O).

For **12c**: mp 118–119°C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.90 (t, J=7.3 Hz, 3H, $(CH_2)_3\underline{Me}$), 1.25 (t, J=7.3 Hz, 3H, $CH_2\underline{Me}$), 1.34 (m, 2H, $CH_2CH_2\underline{CH_2}Me$), 1.89 (m, 2H, $CH_2\underline{CH_2}CH_2Me$), 3.20 (q, J=7.3 Hz, 2H, $\underline{CH_2}Me$), 3.50 (s, 3H, 6-Me), 3.91 (s, 3H, 8-Me), 4.41 (q, J=7.3 Hz, 2H, $\underline{CH_2}CH_2CH_2Me$), 7.52 (s, 1H, 2-H); IR (KBr): 1658, 1707 cm^{-1} (C=O).

For **12d**: mp 235–236°C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.70 (s, 3H, 1-Me), 3.52 (s, 3H, 6-Me), 4.04 (s, 3H, 3-Me), 4.09 (s, 3H, 8-Me), 7.71 (s, 1H, 2-H); IR (KBr): 1655, 1700 cm^{-1} (C=O).

For **12e**: mp 199–201°C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.94 (t, J=7.4 Hz, 3H, $CH_2CH_2\underline{Me}$), 1.99 (m, 2H, $CH_2\underline{CH_2}Me$), 3.52 (s, 3H, 6-Me), 3.95 (s, 3H, 8-Me), 4.46 (q, J=7.3 Hz, 2H, $\underline{CH_2}CH_2Me$), 7.21 (d, J=3.1 Hz, 1-H), 7.73 (d, J=3.1 Hz, 2-H); IR (KBr): 1660, 1700 cm^{-1} (C=O).

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