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A novel one-pot, three-component reaction: formation of tricyclic 1,2-dihydropyridines via mesomeric betaines

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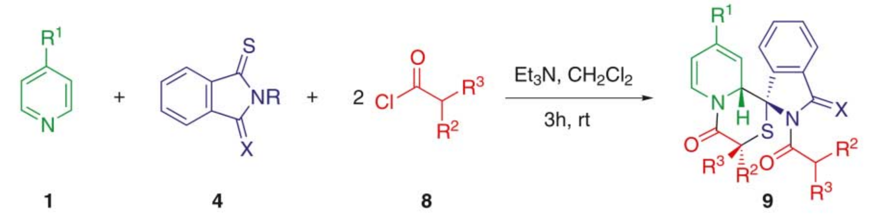
Abstract—A one-pot, three-component reaction of pyridine, thiophthalimide and acyl chloride gives novel tricyclic 1,2-dihydropyridines regio- and stereoselectively, in which a mesomeric betaine would be a key intermediate for [4+2]-cycloaddition reaction with thiocarbonyl compounds.

One-pot, multi-component reactions continue to be of great interest in the synthesis of various compounds containing particularly nitrogen atoms[1] owing to the fast assembly of poly-substituted systems without isolation of unstable intermediates. The importance of these one-pot reactions in such syntheses has been demonstrated in the Mannich, Ugi,[1a,2] Biginelli,[1b] and aza-Baylis–Hillman[3] reactions, and in Hantzsch dihydropyridine synthesis.[4]

During our attempted synthesis of *N*-acyldithiophthalimides, as part of continuing research program of structural studies of twisted amides,[5] we unexpectedly obtained an tricyclic 1,2-dihydropyridine as a major product (Scheme 1). This suggests that a mesomeric betaine,[6] produced from *N*-acylpyridinium salt, would be a key intermediate that undergoes [4+2]-cycloaddition reaction with a thiocarbonyl group. In this communication, we describe a new one-pot, three-component reaction leading to tricyclic 1,2-dihydropyridines.

The reaction of pyridine (**1**), dithiophthalimide (**4**) and 2 equiv. of propionyl chloride (**8b**) in the presence of Et_3N gave tricyclic compound **9b** in 62% yield (Table 1),[7,8] the structure of which was determined by ^1H and ^{13}C NMR and IR spectra, and X-ray crystallographic analysis. Figure 1 shows the ORTEP drawing,[9] which



1 : $R^1 = H$
2 : $R^1 = Me$
3 : $R^1 = NMe_2$

4 : X = S, R = H
5 : X = O, R = H
6 : X = O, R = COEt
7 : X = O, R = Me

8-13
a : $R^2, R^3 = H$
b : $R^2 = Me, R^3 = H$
c : $R^2, R^3 = Me$

9 : X = S, $R^1 = H$
10 : X = O, $R^1 = H$
11 : X = S, $R^1 = Me$
12 : X = O, $R^1 = Me$
13 : X = O, $R^1 = NMe_2$

Scheme 1.

Keywords: one-pot, three-component reaction; mesomeric betaine; 1,2-dihydropyridine; [4+2]-cycloaddition reaction; heterocyclic compound.

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Table 1. One-pot, three-component reactions of pyridine, thiophthalimide and acyl chloride

Entry	Pyridine	Phthalimide	Acyl chloride	Product	Yield (%)[a]
1	**1**	**4**	**8a**	**9a**	19
2	**1**	**4**	**8b**	**9b**	62
3	**1**	**4**	**8c**	**9c**	18
4	**1**	**5**	**8b**	**10b**	60
5	**2**	**4**	**8b**	**11b**	49
6	**2**	**5**	**8b**	**12b**	27
7	**3**	**5**	(Ac_2O)	**13a**	40[b]
8	**1**	**6**	**8b**	**10b**	61
9	**1**	**7**	**8b**	nr	0

[a] Isolated yields.

[b] Yields based on ^1H NMR spectroscopy.

clearly reveals that it consists of 1,2-dihydropyridine, six-membered lactam and *N*-acyl spirothiolactam moieties. Characteristic stereochemical features are *trans* relationship between 2-H of the dihydropyridine moiety and the methyl group in the six-membered lactam ring, and *syn* orientation between the dihydropyridine and the phenyl ring. An additional important feature is that the sulfur atom is incorporated into the six-membered ring at the β-position of the carbonyl group. Surprising is that the reaction provided an almost single product despite having three stereogenic centers.[7]

To elucidate the generality of this one-pot reaction, we employed several pyridine, acyl chloride and phthalimide analogues. The three-component reactions proceeded smoothly in dichloromethane at rt, and were completed within 1–3 h. Table 1 lists the results of the reactions. The reactions with acetyl chloride and isobutyryl chloride gave the corresponding adducts **9a** and **9c** with relatively lower yields than in the case using propionyl chloride (entries 1 and 3). The reaction of monothiophthalimide (**5**) having both a carbonyl and a thiocarbonyl group afforded **10b** containing the sulfur atom in the lactam ring (entry 4), indicating the higher reactivity of the thiocarbonyl than that of the carbonyl group.[10] The structure of the product **9c** was also confirmed to have the same framework as that of **9b** by X-ray analysis.[11]

When 4-methylpyridine (**2**) was used as a substituted pyridine, similar adducts **11b** and **12b** were obtained in 49% and 27% yields, respectively (entries 5 and 6). The reaction of 4-dimethylaminopyridine (**3**) with an acyl chloride gave no expected product, but acetic anhydride was effective to give **13a** in 40% yield (entry 7).

Despite using *N*-propionylmonothiophthalimide (**6**) instead of **5** in the case of entry 4, the same compound **10b** was obtained in 61% yield (entry 8). On the other hand, no product was observed in the reaction of *N*-methylmonothiophthalimide (**7**) (entry 9). These results indicate a necessity of the *N*-acyl group in this cyclization reaction.

It may be noted that upon heating the product **9b** at 60°C for 3 h, *N*-propionyldithiophthalimide (**14**) and dithiophthalimide (**4**) were produced in 29% and 59% yields, respectively, which seems to be a result of reverse cycloaddition reaction (Scheme 2). Formation of no regio- and stereoisomers in this one-pot reaction also suggest the participation of a cycloaddition reaction. These results led us to presume that a mesomeric betaine **A** would be a key intermediate (Scheme 3). The formation of a similar betaine has been reported in the reaction of pyridine with ketene[12] and was postulated during some cyclization reactions.[6,13] Since mesomeric betaines have been known to behave as 1,3-dipoles, the postulated betaine and the thiocarbonyl group would undergo a cycloaddition reaction. The observed higher reactivity of the thiocarbonyl than that of the carbonyl group is in agreement with the general feature of significant reactivity of thiocarbonyl compounds in the cycloaddition reaction.[10]

A plausible pathway that satisfies all of the foregoing results is shown in Scheme 3. The key intermediary betaine may arise either from *N*-acylpyridinium with Et_3N or directly from pyridine and a ketene produced

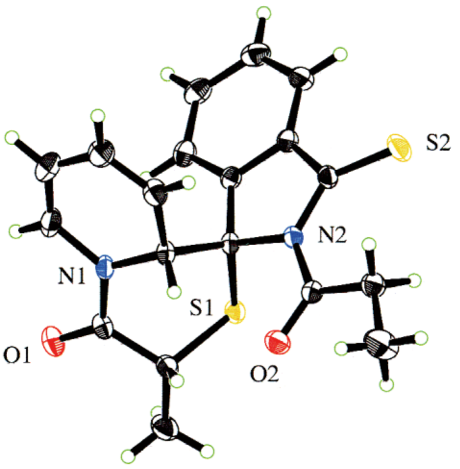
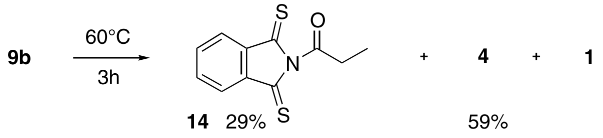
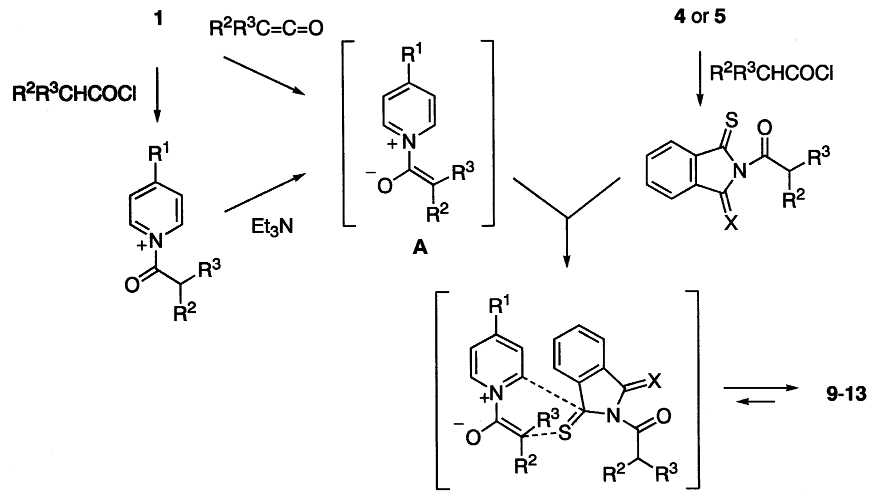


Figure 1. ORTEP drawing of **9b** at the 30% probability level.



Scheme 2.



Scheme 3.

from an acyl chloride. The betaine reacts with N-acyldithiophthalimide to afford a six-membered lactam ring via [4+2]-cycloaddition reaction,[14] which results in *trans* stereochemistry between 2-H and the methyl group. The *syn* orientation about the dihydropyridine ring and the phenyl group may be due to intermolecular cation-π interaction[15,16] of the pyridinium cation with the π-electron of the aromatic moiety of N-acylthiophthalimide in the cyclization step.

In summary, we have found a new one-pot, three-component reaction of thio- or dithiophthalimide, a pyridine derivative and an acyl chloride leading to a novel tricyclic 1,2-dihydropyridine derivative. The key step in this reaction presumably involves [4+2]-cycloaddition reaction of the mesomeric betaine with a thiocarbonyl group.

Acknowledgements

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7. The ^{1}H NMR spectrum of the crude products shows only one stereoisomer in high yield. The yield seems to significantly diminish during the purification.
8. *General experimental procedure*: To a solution of a 1:1 mixture of pyridine (24 μl, 0.3 mmol), dithiophthalimide (53.5 mg, 0.3 mmol) and Et_3N (125 μl, 0.9 mmol) in CH_2Cl_2 was added 2 equiv. of propionyl chloride (52 μl, 0.6 mmol) at 0°C and the solution was stirred for 3 h at rt. After addition of satd $NaHCO_3$ solution, the reaction mixture was extracted three times with CH_2Cl_2 (3×5 ml), and the combined extract was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude compound, which was subjected to silica gel column chromatography using a 6:1 mixture of hexane and ethyl acetate as an eluent to yield pure **9b** as a solid (69.2 mg, 0.187 mmol).
9. *Crystal data*: Compound **9b**: $C_{19}H_{18}N_2O_2S_2$, $M = 370.47$, monoclinic, $P2_1/a$, $\mu = 2.897$ mm^{-1}, $a = 15.193(2)$, $b = 8.7767(9)$, $c = 13.2074(13)$ Å, $\beta = 98.589(8)°$, $V = 1741.4(3)$ Å^3, $T = 293$ K, $Z = 4$, $D_{\mathrm{calcd}} = 1.413$ g cm^{-1}, a total of 3376 reflections were collected and 3169 are unique ($R_{\mathrm{int}} = 0.0328$). R_1 and wR_2 are 0.0403 [$I > 2\sigma(I)$] and 0.1397 (all data), respectively. CCDC 207126.
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11. Compound **9c**: $C_{21}H_{22}N_2O_2S_2$, $M = 398.53$, monoclinic, $P2_1/n$, $\mu = 2.543$ mm^{-1}, $a = 31.501(4)$, $b = 7.515(2)$, $c = 17.356(3)$ Å, $\beta = 101.510(12)°$, $V = 4026.0(13)$ Å^3, $T = 293$ K, $Z = 8$, $Dc = 1.315$ g cm^{-1}, a total of 6098 reflections were collected and 5976 are unique ($R_{\mathrm{int}} = 0.0219$). R_1 and wR_2 are 0.0382 [$I > 2\sigma(I)$] and 0.1796 (all data), respectively. CCDC 207127.
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