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Novel thermal iminocyclopropene rearrangements: regioselectivity in the synthesis of pyrroles

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Abstract—A novel and readily available method for synthesis of pyrroles possessing substituents with various functional groups has been developed, by means of thermal iminocyclopropene rearrangements. It will provide a novel and readily available access to pyrroles under mild reaction conditions with simple procedures. The regioselectivity in this iminocyclopropene rearrangement was disclosed.

A cyclopropene skeleton exists at a rather highly activated energy level in its ground state, owing to its intrinsic severe steric strain, and, therefore, it has been well known to be limited to access to it synthetically.[1] Currently, a new and readily available method has been communicated for access to cyclopropenes by the assistance of rhodium catalysts.[2] We wish to communicate herein a novel, simple, and synthetically available approach to pyrroles involving substituents with various functional groups under mild reaction conditions by means of novel thermal rearrangements of iminocyclopropenes.[3] Heterocyclic chemistry of pyrroles plays a significant role in the areas of pharmaceutical sciences and organic synthesis,[4] ranging from medicines to material sciences such as ligands in catalytic (asymmetric) synthetic reactions.[5]

In comparison with cyclopropane chemistry, which has had a long history of research of theoretical interest and synthetic uses,[6] especially in the pharmaceutical area, a cyclopropene seems to be a more labile and reactive chemical species, and therefore, we expect it might be a more chemically interesting and synthetically useful intermediate. For instance, for thermal cleavage of a cyclopropane ring, rather or very severe heating at high temperature is required normally. An iminocyclopropane–dihydropyrrole rearrangement also needs heating at considerably high temperature (130–140 °C) even though by the assistance of an acid catalyst such as ammonium chloride or hydrobromic acid.[7]

On the other hand, a cyclopropene ring can be shown to be more reactive, due to the strain involved in the ring, resulting in smooth opening of the ring under rather mild reaction conditions, followed by rearrangement or cycloaddition reactions to yield five-membered carbo- or heterocycles, or other cyclic products.

An iminocyclopropene–pyrrole rearrangement, however, which has been developed by us, proceeds at much lower reaction temperature (60–80 °C) without any assistance by catalysts; the yield and regioselectivity of the products depend upon the reaction solvent used and the reaction temperature.

The thermal rearrangements of iminocyclopropenes (imine IR: 1651 cm^{-1}) into pyrroles were studied by reacting ketoesters **1a**[2] with primary amines **2c** in toluene at 40–110 °C in the presence of molecular sieves 4 Å to afford pyrroles **4c** and **5c** and the results are summarized (Scheme 1 and Table 1).

As shown in Table 1, the highest yield (72%) of **4c** and **5c** was obtained with a 94:6 ratio of **4c** and **5c**, respectively, by the reaction of **1** with 5.0 equiv of benzylamine (**2c**) in toluene at 80 °C for 12 h in the presence of molecular sieves 4 Å. Use of a lower amount of benzylamine (3.0 equiv) in the above reaction gave **4c** and **5c** in 43% yield with a lower ratio of **4c** to **5c** (80:20). The reaction

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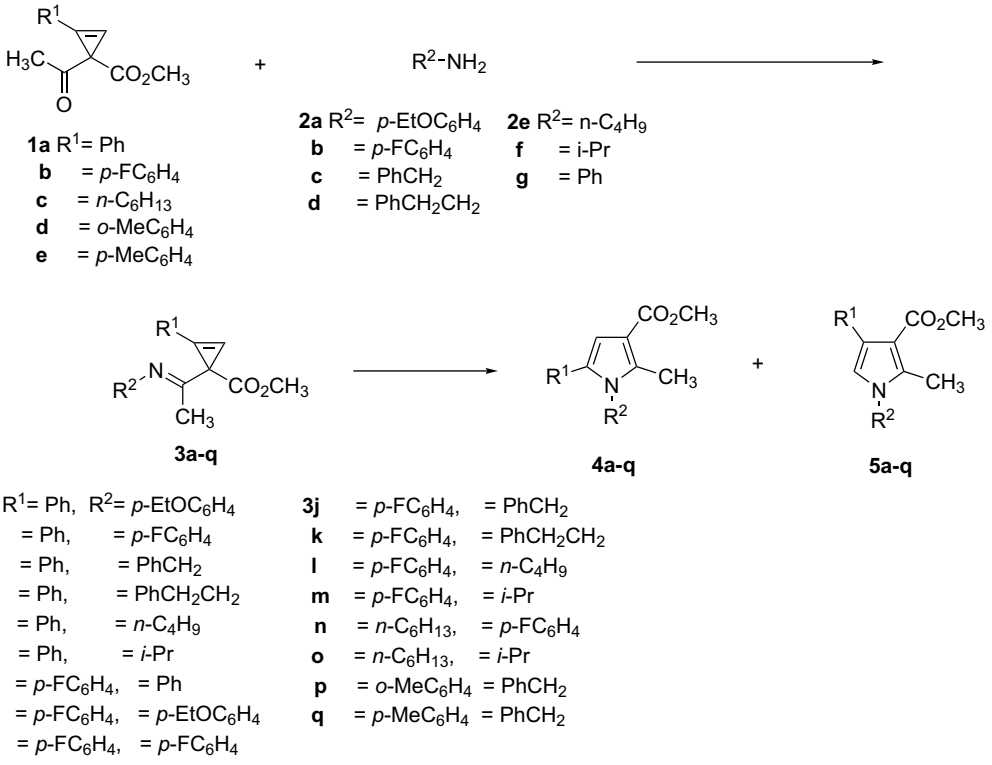


Scheme 1.

Table 1. Studies on thermal rearrangements of iminocyclopropenes **3c** into pyrroles (**4c** and **5c**)

Entry	$C_6H_5CH_2NH_2$ (equiv)	Solvent	Temp (°C)	Time (hr)	**4c**:**5c**[a]	Yields (%)
1	1	Toluene	60	39	83:17	15 (80)[b]
2	3	Toluene	60	17	80:20	43
3	5	Toluene	40	20	91:9	50
4	5	Toluene	60	14	93:7	70
5	5	Toluene	80	12	94:6	72
6	5	Benzene	Reflux	12	94:6	55
7	5	Xylene	80	12	97:3	48
8	5	$CHCl_3$	Reflux	12	93:7	57
9	5	CH_2Cl_2	Reflux	24	98:2	65[c] (33)[b]
10	5	HMPA	80	12	91:9	52
11	5	CH_3CN	Reflux	12	74:26	54
12	5	DMA	80	12	31:69	35
13	5	DMSO	80	12	23:77	23
14	5	DMF	80	12	23:77	29

[a] The ratio was determined by ^1H NMR analysis.
[b] Yields of the recovered starting material.
[c] A corrected yield based on the recovered starting material.

of **1a** with a stoichiomeric amount of benzylamine provided products **4c** and **5c** in a poor yield (15%) with the recovered starting material (80%).

Stereoelectronic effects of substituents on the cyclopropenes were studied (Table 2). Initially, effects of aromatic substituents were examined using phenyl, *p*-tolyl, *o*-tolyl, or *p*-fluorophenyl groups as a substituent. A cyclopropene (**3c**) possessing a phenyl group as a substituent on the ring underwent a smooth thermal reaction (in toluene at 80 °C for 12 h) to give pyrroles **4c** and **5c** in good yields (72%). The reaction of *p*-substitution models (**3j** and **3q**) on the phenyl ring provided corresponding pyrroles (**4j**, **4q** and **5j**, **5q**) with a similar ratio of **4** and **5**, however the chemical yields were dependent upon the stereoelectronic effects of the substituents. In the case of *p*-fluorophenyl (**3j**) or *p*-tolyl (**3q**) group, the chemical yields were decreased (43% and 18%) by lowering of reactivity of alkenyl carbocations **6** due to stabilization by resonance effects by a *p*-fluoro group or electron donating effects by a *p*-methyl group in **6**. On the other hand, in the case of **3p** (*o*-tolyl substituent), the reaction via **6** would be more preferable giving high regioselectivity (>99:1), since another intermediate (**7**) has severe steric hindrance between the *o*-tolyl and the methyl ester groups.

Table 2. Thermal rearrangements of iminocyclopropenes **3** into pyrroles (**4** and **5**)

Entry	R^1	R^2	Products	Ratio of **4**:**5**[a]	Yields (%)
1	Ph	*p*-$EtOC_6H_4$	**4a/5a**	90:10	75
2	Ph	*p*-FC_6H_4	**4b/5b**	92:8	53
3	Ph	$PhCH_2$	**4c/5c**	94:6	72
4	Ph	$PhCH_2CH_2$	**4d/5d**	95:5	46
5	Ph	*n*-C_4H_9	**4e/5e**	91:9	67
6	Ph	*i*-Pr	**4f/5f**	25:75	36
7	*p*-FC_6H_4	Ph	**4g/5g**	93:7	56
8	*p*-FC_6H_4	*p*-$EtOC_6H_4$	**4h/5h**	91:9	33
9	*p*-FC_6H_4	*p*-FC_6H_4	**4i/5i**	93:7	44
10	*p*-FC_6H_4	$PhCH_2$	**4j/5j**	97:3	43
11	*p*-FC_6H_4	$PhCH_2CH_2$	**4k/5k**	94:6	43
12	*p*-FC_6H_4	*n*-C_4H_9	**4l/5l**	91:9	53
13	*p*-FC_6H_4	*i*-Pr	**4m/5m**	10:90	24
14	*n*-C_6H_{13}	$PhCH_2$	**4n/5n**	58:42	80
15	*n*-C_6H_{13}	*i*-Pr	**4o/5o**	12:88	64
16	*o*-MeC_6H_4	$PhCH_2$	**4p/5p**	>99:1	21
17	*p*-MeC_6H_4	$PhCH_2$	**4q/5q**	95:5	18

[a] The ratio was determined by ^1H NMR analysis.

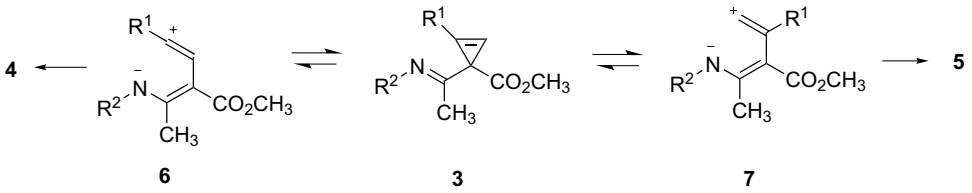
In the case of **3n** (*n*-hexyl substituent), the reaction via **6** would slightly decrease due to steric reason by the *n*-hexyl group to give pyrroles **4n** and **5n** with a ratio of 58:42, respectively.

Dramatic solvent effects were observed in the above reaction (Table 1). We examined solvent effects, by employing, instead of toluene, acetonitrile, chloroform, dichloromethane, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), benzene, xylene, *N*,*N*-dimethylacetamide (DMA), or HMPA as a solvent. The results are summarized in Table 1. As listed in Table 1, it should be noted that inversion of the regioselectivity in the product was observed, depending upon the solvent used. With the use of a slightly or strongly polar solvent such as acetonitrile, DMSO, or DMF, an amount of **5c** was increased in acetonitrile with a 74:26 ratio of **4c** and **5c**, and **5c** was obtained as a major product in DMSO, DMF and DMA with 23:77 to 31:69 ratio of **4c** and **5c**, respectively, even though the yield was not so high (54–23%). In another case using **3e** in DMSO, the inversion of regiochemistry in products was observed with the same ratio (**4e**:**5e** = 8:92, 30% yield).

Use of other primary amines (**2a**–**g**) (5.0 equiv), instead of benzylamine, in the above reaction was studied under the same reaction conditions (in toluene, 80 °C, and 12 h), and the results are listed in Table 2. It shows that moderate yields of **4a**–**q** and **5a**–**q** were obtained with high regioselectivity (75:25 to >99:1). The steric bulkiness of N-substituents at the imino groups seriously affected the cyclization stage. We have studied the effects of N-substituents in **3**, changing the substituents such as benzyl, phenethyl, *p*-methoxyphenyl, *p*-fluorophenyl, *n*-butyl, *i*-propyl and phenyl groups. As we expected, no big difference was observed in the series of aromatic substituents and alkyl substituents. However, it should be noted that the regiochemistry of the products was inversed in the case of *i*-propyl group as shown in Table 2. An *i*-propyl group significantly affected the regiochemistry on cyclization, with the preferential formations of **5f** over **4f** (75:25) and **5m** over **4m** (90:10) (Table 2).

The structure of the products **4** and **5** was determined by the NMR spectral analysis. The α-methylene of benzyl group, methyl ester at C3 and methyl at C2 of **5c** appear at 5.07, 3.67 and 2.45, respectively.[8] The hydrogens at C5 of **5g** and C4 of **4g** appear at 6.68 and 6.74, respectively.[9] The regiochemistry of **4g** was determined by NOE observed between a hydrogen at C4 and a methoxy group, and also HMBC between the hydrogen at C4 and the ester carbonyl carbon. The regiochemistry of the product **4m** and **5m** was determined by NMR spectral analysis; the hydrogens at C5 of **5m** and C4 of **4m** appear at 6.60 and 6.43, respectively.[9]

The experimental results obtained, including the regioselectivity and the solvent effects mentioned above, are rationalized as follows. If the reaction proceeds via a concerted mechanism, it will be particularly hard to rationalize the dramatic solvent effects mentioned above. Therefore, on the basis of this fact, we can undoubtedly anticipate the existence of ionic intermediates such as **6** and **7**, which are formed by fission of the cyclopropene rings, followed by cyclization affording **4** and **5**, respectively. In the cyclization, if the steric factors are seriously important, the thermal reaction will provide **5** as a major product. Otherwise, if the chemical stability of the intermediary sp^2 carbocation is a crucial factor for cyclization, **4** will be provided as a major product. Based on the results described earlier, it should be concluded that the most important factor in this reaction will be the stability of the sp^2 carbocation produced. So, with the use of DMSO and DMF as a solvent, steric interference will be increased by solvation of the carbocation coordinated with the anionic solvents to disturb the reaction at the stage **6**, and, therefore, the formation of **5** will be preferred with the solvent. However, the use of HMPA as a solvent was not effective for presentation of high regioselectivity, due to decrease of the coordination ability to alkenyl carbocations presumably by the steric reason. The steric effects by N-substituent (*i*-propyl) in the imino groups will be rationalized along this line (Scheme 2).



Scheme 2.

Thus, we have developed a novel and readily available method for synthesis of pyrroles with various groups via thermal rearrangement of iminocyclopropenes into pyrroles. We have determined the regiochemistry at the cyclization by the effects of substituents in the systems, and disclosed regioselectivity and also dramatic solvent effects in this rearrangement. Based on the regiochemical results, the reaction mechanism is discussed.

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