SYNTHETIC STUDY DIRECTED TOWARD NOVEL MULTI-LINKED HETEROCYCLES [1]

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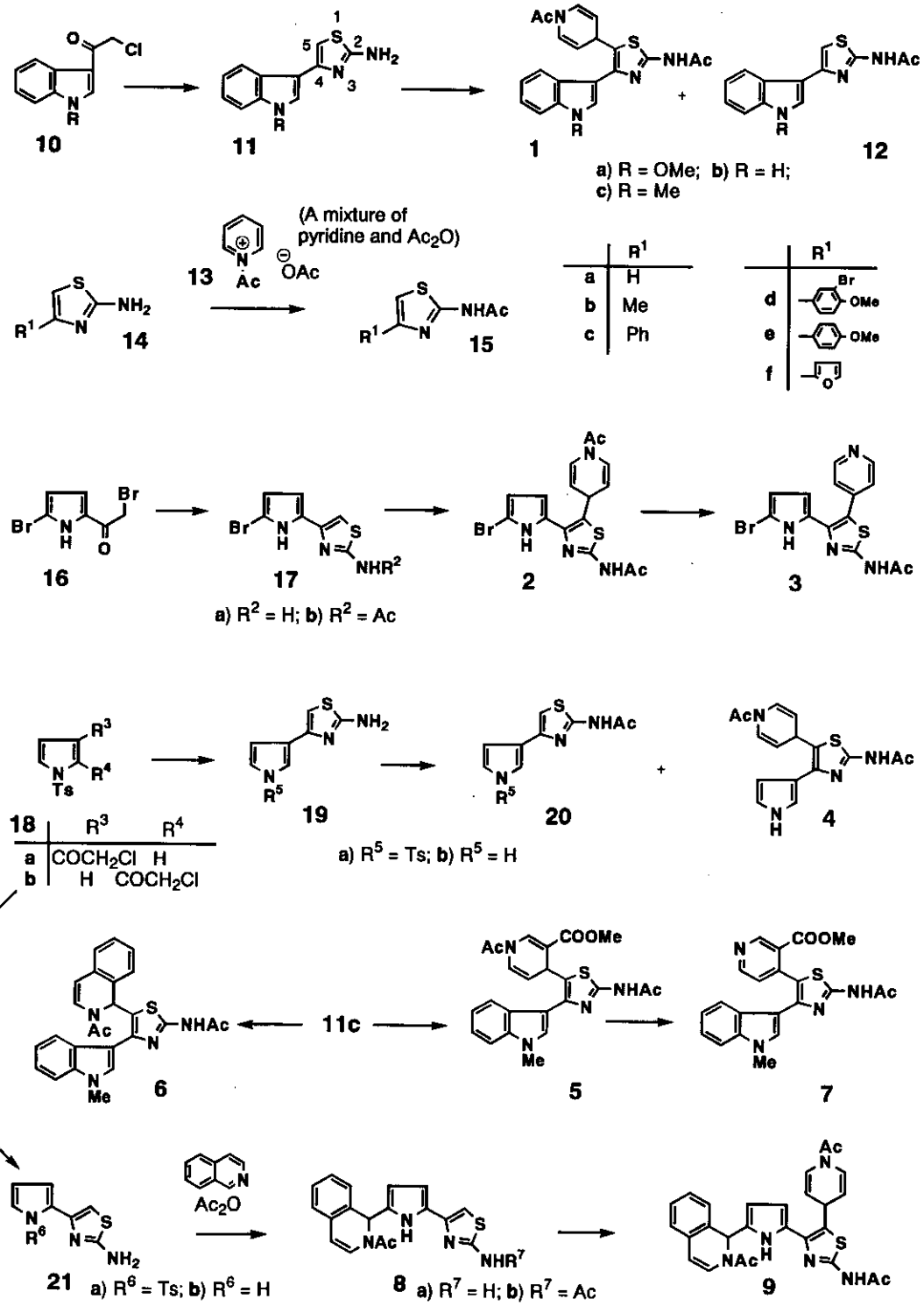
Abstract ——— 2-Amino-4-(1-methylindol-3-yl)thiazole (**11c**) has a characteristic nucleophilic nature at the 5-position and add to the 4-position of acetylpyridinium acetate (**13**) producing 2-acetylamino-5-(1-acetyl-1,4-dihydropyridin-4-yl)-4-(1-methylindol-3-yl)-thiazole (**1c**). *Its structure was established by X-ray single crystallographic analysis.* Applying the results, simple syntheses of the related tris- (**1a-b** and **2-8**) and tetrakis-linked heterocycles (**9**) were achieved.

A variety of heterocyclic compounds have biological activities.[2] In order to develop new lead compounds, we have designed a novel type of compounds which are consisted of plural heterocycles connected each other through single bond. We can classify these compounds as multi-linked heterocycles. In this communication, we wish to report the syntheses of tris- (**1a-c** and **2-8**) and tetrakis-linked heterocycles (**9**) including indole, isoquinoline, pyridine, pyrrole, and thiazole as a component of heterocycles.

3-Chloroacetyl-1-methoxyindole (**10a**), prepared from 1-methoxyindole[3] in 80% yield according to our procedure,[3a] was converted to 4-(1-methoxyindol-3-yl)-2-aminothiazole (**11a**, 68%) by the reaction with thiourea. Similarly, 3-chloroacetylindole (**10b**) and -1-methylindole (**10c**) were converted to the corresponding **11b** (95%) and **11c** (94%). Interestingly, their 5-positions of 2-aminothiazole part were newly found to have a characteristic nucleophilic character. Thus, when **11a** was treated with a mixture of pyridine and acetic anhydride (Ac_2O) at room temperature, tris-linked heterocycle, 2-acetylamino-5-(1-acetyl-1,4-dihydropyridin-4-yl)-4-(1-methoxyindol-3-yl)thiazole (**1a**), was produced in 36% yield together with **12a** (55%). Under similar reaction conditions, **11b** and **11c** produced **1b** (65%) and **1c** (42%) in addition to **12b** (34%) and **12c** (46%), respectively.

The above results are remarkable findings because acetylpyridinium acetate (**13**, *in situ* formation upon mixing pyridine and Ac_2O) has not been reported to react at the pyridine part with nucreophiles except one case.[4] Based on this character, **13** has long been utilized as acetylating reagent combining pyridine and Ac_2O. In order

Scheme 1


10
11
1
12
a) R = OMe; b) R = H;
c) R = Me
(A mixture of
pyridine and Ac2O)
13
14
15
16
17
a) R2 = H; b) R2 = Ac
2
3
18
19
20
4
a) R5 = Ts; b) R5 = H
11c
6
5
7
21
a) R6 = Ts; b) R6 = H
8
a) R7 = H; b) R7 = Ac
9

to clarify the reactivity of 5-position of 2-aminothiazoles, reactions of **13** with **14a-f** were examined. The results were exclusive formations of 2-acetylaminothiazoles (**15a-f**). Surprisingly, formations of **1** type tris-linked compounds were not detected at all in every case.

The structure of **1c** was determined by X-ray single crystallographic analysis and the results are shown in Figure 1. 5-Bromo-2-bromoacetylpyrrole (**16**) afforded 2-aminothiazole (**17a**, 94%), which reacted with pyridine and Ac_2O to afford **2** (34%) and **17b** (47%). DDQ oxidation of **2** successfully transformed 1,4-dihydropyridine part to pyridine and 2-acetylamino-4-(5-bromopyrrol-2-yl)-5-(pyridin-4-yl)thiazole (**3**) was produced in 93% yield. Similarly, 3-chloroacetyl-1-tosylpyrrole (**18a**) was converted to 2-aminothiazole (**19a**, 96%). The reaction of **19a** with pyridine and Ac_2O afforded 2-acetylaminothiazole (**20a**, 94%) as a sole product. Under the same reaction conditions, *N*-unsubstituted pyrrole (**19b**), obtained in 72% yield by alkaline hydrolysis of **19a**, generated a tris-linked heterocycle (**4**, 39%) in addition to **20b** (59%).

Figure 1.
ORTEP Drawing of **1c**

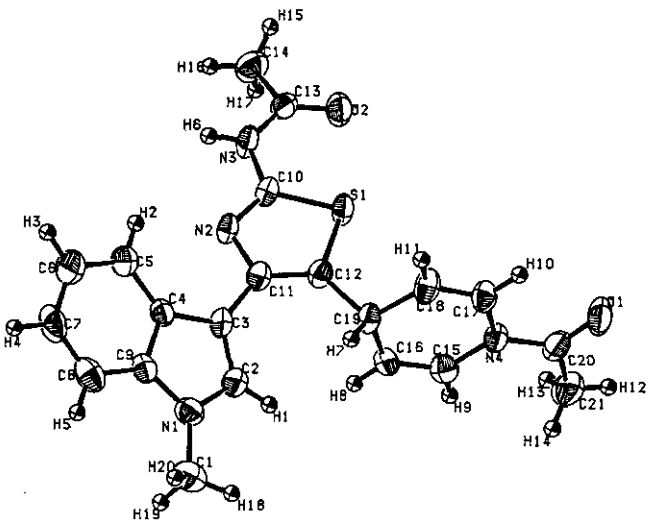


Table 1.
δ-Value of 5-Position of 2-Aminothiazoles in the ^{13}C-NMR Spectra

Compounds	δ-Value (ppm)
21b	98.30
19b	98.36
17a	99.58
11c	99.36
11b	99.61
11a	100.26
Addition to **13** occurs.	

Compounds	δ-Value (ppm)
14d	101.67
19a	101.73
14b	102.00
14f	102.10
21a	108.51
Addition to **13** does not occur.	

The electron density of the 5-position seem to govern the reactivities of 2-aminothiazoles. Thus, the reaction with **13** occurred only in the cases where δ-values of the 5-position in their ^{13}C-NMR spectra, summarized in Table 1, are lower than 101 ppm. These results clearly suggest that 2-amino and 4-indolyl or 4-pyrrolyl groups on the thiazole nucleus cooperate to increase the electron density of the 5-position, and turn it to a soft nucleophile.

The above soft nucleophiles could also react with other iminium salts.[5] For example, **11c** reacted with methyl nicotinate in Ac_2O to produce **5** (61%) and **12c** (38%), while the reaction with isoquinoline and Ac_2O afforded **6** (90%) and **12c** (8%). Further treatment of **5** with DDQ afforded **7** in 77% yield.

4-(Pyrrol-2-yl)-2-aminothiazole (**21b**), obtained from **18b** through **21a** in 57% overall yield by a sequential reaction with thiourea and subsequent hydrolysis, was an interesting substrate. When **21b** reacted with isoquinoline and Ac_2O, the amino group and the 5-position of thiazole were completely inert and only α-position of pyrrole reacted to produce **8a** (82%). The compound (**8a**) could further react with pyridine and Ac_2O to give **8b** (45%) and the desired tetrakis-linked heterocycle, 2-acetylamino-5-(1-acetyl-1,4-dihydropyridin-4-yl)-4-[5-(2-acetyl-1,2-dihydroisoquinolin-1-yl)pyrrol-2-yl]thiazole (**9**, 40%).

In conclusion, we found that some of 2-aminothiazoles have an excellent nucleophilic nature at the 5-position and add even to acetylpyridinium acetate giving 1,4-dihydropyridines. Utilizing this novel reaction, simple synthesis method for various multi-linked heterocycles was developed.

REFERENCES AND NOTES

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5. Reactions with other various iminium salts were examined extensively. The results will be reported in due course.

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