Mixed Heteroarene Oligomers

Akio Minato,*[a] Keizo Suzuki,[a] Kohei Tamao,*[b] and Makoto Kumada[b]

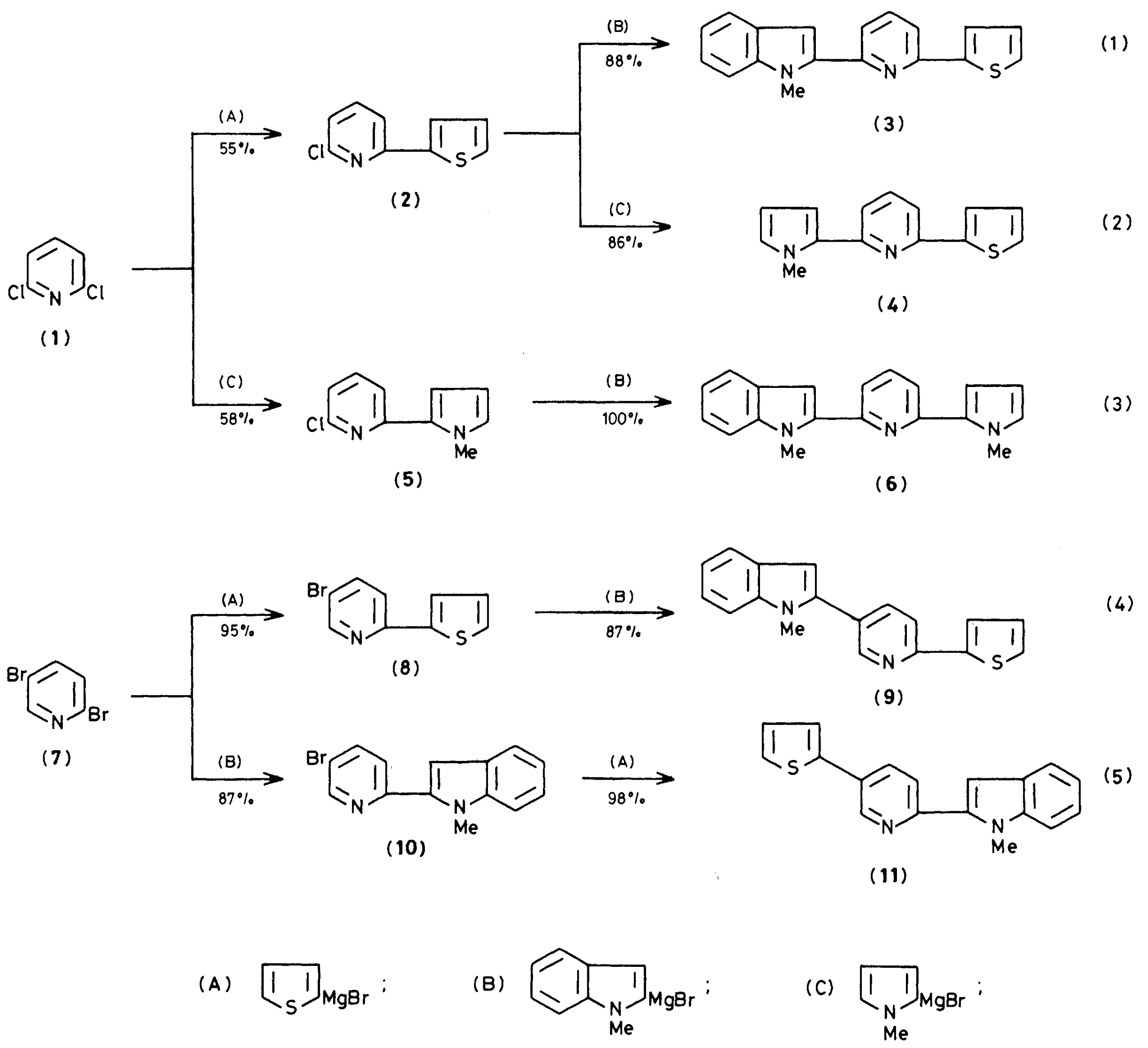
[a] *Kyoto College of Pharmacy, Misasagi, Yamashina, Kyoto 607, Japan*
[b] *Department of Synthetic Chemistry, Kyoto University, Kyoto 606, Japan*

Various types of mixed heteroarene oligomers can be readily prepared from heteroarene dihalides *via* stepwise coupling with heteroaryl Grignard reagents catalysed by a palladium–phosphine complex.

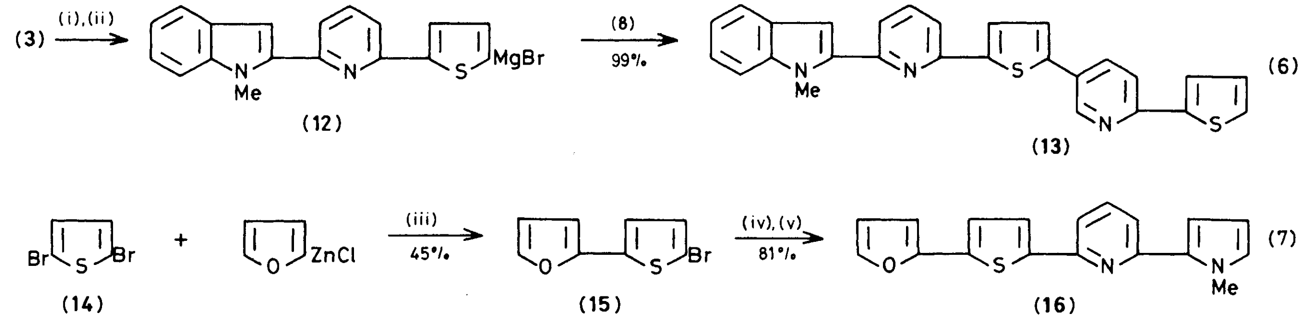
The chemistry of mixed heteroarene oligomers is an area of heterocyclic chemistry which remains to be explored in detail.[1—4] Apart from Kauffmann's pioneering work,[1] there has been little development. While mixed heteroarene dimers are common in the literature,[5—7] there is little information on mixed heteroarene trimers, and much less on higher oligomers, especially when the heteroarene components are all different, or connected at different positions.[1,2,7] This is apparently due to the lack of an efficient preparative method.

We describe herein a new, general, and straightforward method for the synthesis of various types of mixed heteroarene oligomers. The method consists of a stepwise heteroarylation of heteroarene dihalides *via* cross-coupling reactions with heteroaryl Grignard reagents in the presence of a palladium–phosphine complex as a catalyst.[6] The key step is the first example of the selective mono-heteroarylation of dihalides.[8]

Representative results, shown in equations (1)—(5), Scheme 1, have been obtained for the preparation of a variety of mixed heteroarene trimers from dihalogenopyridines, (**1**) and (**7**), in combination with the three heteroaryl Grignard reagents (A), (B), and (C). In each coupling step, $PdCl_2$-



Scheme 1



Scheme 2. *Reagents and conditions:* (i) Bu^{n}Li, THF; (ii) MgBr$_2$; (iii) room temp., 2 h; (iv) Mg, diethyl ether; (v) (**5**), reflux, 22 h.

(dppb) (dppb = Ph$_2$P[CH$_2$]$_4$PPh$_2$) was used as a catalyst (*ca.* 1 mol %). Typically, 2,6-dichloropyridine (**1**) was allowed to react with 2-thienylmagnesium bromide (A) (1 equiv.) in the presence of the palladium catalyst to give 2-chloro-6-(2-thienyl)pyridine (**2**), (m.p. 39—41 °C, 55% yield). The subsequent reaction of the dimer halide (**2**) with 1-methyl-2-indolylmagnesium bromide, (B)^6 (1.5 equiv.) proceeded smoothly in refluxing tetrahydrofuran (THF) over 1 h to give the trimer, 2-(1-methyl-2-indolyl)-6-(2-thienyl)pyridine (**3**) (m.p. 131—131.5 °C, 88% yield). The reaction of 1-methyl-2-pyrrolylmagnesium bromide (C)^6 with (**2**) afforded a different trimer (**4**) (m.p. 53—54 °C, 86% yield). A trimer consisting of three different nitrogen heteroarenes (**6**) (m.p. 123—124 °C) was also obtained from (**1**) in two steps. These results demonstrate that it is possible to introduce, in successive steps, different types of heteroaryl groups into a symmetrical heteroarene dihalide.

When the unsymmetrical dibromide (**7**) was treated with 1 equiv. of (A) at room temperature for 5 h, the dimer halide (**8**) (m.p. 80.5—81.5 °C) was obtained in 95% yield. The reaction of (**8**) with (B) under more vigorous conditions (THF, reflux, 18 h) gave trimer (**9**) (m.p. 126—127 °C, 87% yield). Treatment of (**7**) first with (B), and then with (A), gave trimer (**11**) (m.p. 169—170 °C, 98% yield), a regioisomer of (**9**). Thus, regioisomeric trimers can be prepared from the same starting halide by merely altering the order of addition of the two Grignard reagents.

Further extension of the 'heteroarene chain' is possible. As shown in equation (6), Scheme 2, the trimer Grignard reagent (**12**), prepared readily from (**3**) by lithiation (Bu^nLi, THF)† followed by transmetallation with $MgBr_2$, coupled with (**8**) to give pentamer (**13**) (m.p. 222—224 °C) quantitatively. The tetramer (**16**) (m.p. 120—121 °C) which contains four different heteroarenes, was also readily prepared from 2,5-dibromothiophene [equation (7), Scheme 2].‡

Consequently, the present method can produce mixed heteroarene oligomers by controlling the number, kind, and position of heteroarenes to be connected.

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† In THF solution, metallation of 2-(2-thienyl)pyridine occurs selectively at the α-position of the thiophene ring: P. Ribereau and G. Queguiner, *Tetrahedron,* 1983, **39**, 3593.

‡ All the heteroarene oligomers obtained here, except (**2**), are new compounds and have been fully characterized.

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