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Synthesis of tetrakis(2-pyridyl)methane: the first tetrapyridylmethane

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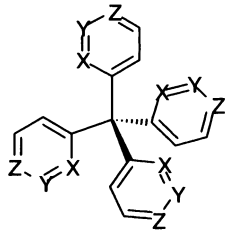
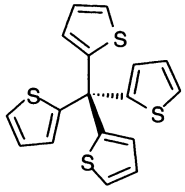
Abstract—Tetrakis(2-pyridyl)methane has been synthesized as the first member of tetrapyridylmethane family by nucleophilic aromatic substitution of 2-chloropyridine with tris(2-pyridyl)methyl anion in refluxing aromatic hydrocarbons; the use of 2-bromopyridine resulted in electron transfer giving rearranged dimer of tris(2-pyridyl)methyl radical.

In view of the basic property and complex-forming ability of sp^2 nitrogen, tetrapyridylmethanes would be intriguing molecules. There can be fifteen positional isomers for tetrapyridylmethane; among them tetrakis(2-pyridyl)-, tetrakis(3-pyridyl)-, and tetrakis(4-pyridyl)methane, **1**, **2** and **3**, which have higher symmetry than the others, would be the key members. Compound **3**, having the highest symmetry, would be an especially useful building block for the construction of tetrahedral networks through complexation with transition metal complexes. However, none of the tetrapyridylmethanes have been synthesized. Here we report the synthesis, X-ray structure, and some properties of **1**, the first member of tetrapyridylmethanes as well as the second member of tetrakis(heteroaryl)methane in general next to tetrakis(2-thienyl)methane **4**.[1]



1, X = N, Y = Z = CH
2, Y = N, X = Z = CH
3, Z = N, X = Y = CH



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Difficulty in the synthesis may be the main reason for the complete absence of tetrapyridylmethanes. Old-known tetraphenylmethane has been synthesized in several ways by taking advantages of the ability of benzene for electrophilic substitutions and fair stability of triphenylmethyl cation.[2] Similar methods seem hardly applicable to tetrapyridylmethanes because pyridine is reluctant to undergo aromatic electrophilic substitutions and tripyridylmethyl cations are all unknown probably due to their electronic instability. Tetrathienylmethane **4** was synthesized by an application of butadiyne-thiophene transformation, where the fourth thiophene ring was constructed from a butadiyne moiety in the molecule. Similar approach seems also not easy for tetrapyridylmethane in the absence of proper way for the intramolecular pyridine ring formation.

One advantageous property of pyridine over benzene from the synthetic point of view is that 2- and 4-halopyridines are susceptible to aromatic nucleophilic substitutions similar to 4-halonitrobenzenes. Therefore, aromatic nucleophilic substitution reactions between tripyridylmethyl anions and 2- or 4-halopyridines would be a possible way for tetrapyridylmethanes despite of some problems lying at the side of the anion. One problem is the steric bulkiness around the anion center (C-α) and another is dispersion of the negative charge into pyridyl groups. Both problems would make the nucleophilic reactivity of the anion weak. Nevertheless, if this approach is successful, it would be applicable to the synthesis of a number of tetrapyridylmethanes including **1** and **3**. Since tris(2-pyridyl)methane **5**[3] is the only compound so far known among tripyridylmethanes and 2-halopyridines are more convenient for handling than 4-halopyridines, we

Keywords: tetrakis(2-pyridyl)methane; tris(2-pyridyl)methyl anion; nucleophilic substitution; electron transfer.

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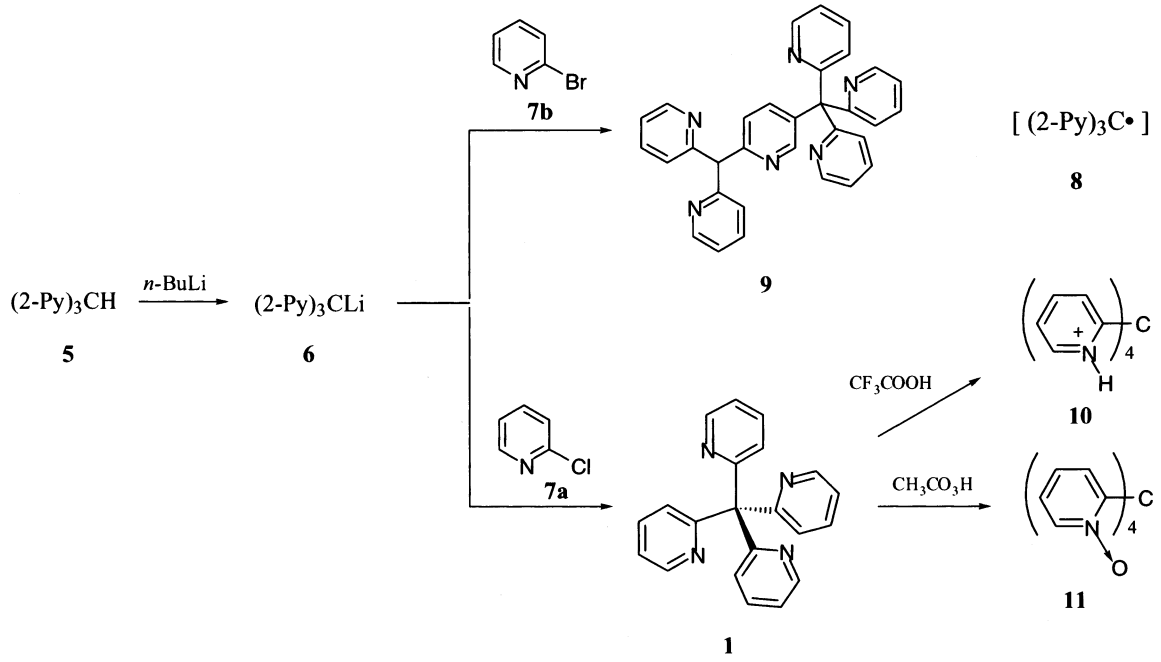


Scheme 1.

at first attempted the synthesis of tetrakis(2-pyridyl)methane **1**.

We examined the reaction of tris(2-pyridyl)methyl anion **6** with 2-bromopyridine **7b** at the beginning. Attempted reaction of **6**, generated by treatment of **5** with *n*-BuLi, with **7b** in THF resulted mostly in the recovery of **5** even after heating to reflux for 90 h under nitrogen atmosphere. However, a reaction occurred under a more drastic condition: heating a mixture of **6** and **7b** (5 equiv.) in toluene to reflux for 48 h gave a mixture from which a dimeric substance **9**[4] was obtained in 10% yield together with **5** (16%) and a small amount of tris(2-pyridyl)methyl alcohol (Scheme 1). The formation of **9** is best explained by hydrogen shift of the primary coupling product of tris(2-pyridyl)methyl radical **8** which is formed by an electron transfer reaction from **6** to **7b**. Next examined was 2-chloropyridine **7a** which is less bulky than **7b** and hence would be more suitable for the nucleophilic substitution, and it was found that the desired compound **1**[5] is obtainable (Scheme 1 and Table 1): the reaction of **6** and **7a** (5 equiv.) in THF at reflux for 24 hours gave **1** in a small amount (entry 1), in toluene at reflux in a higher yield of 6% (entry 2), in xylene at reflux in 28% yield (entry 3), and finally in mesitylene at reflux in a much improved yield of 52% (entry 4). In these reactions, unconsumed tris(2-pyridyl)methane **5** was recovered in good yields.

Tetrapyridylmethane **1** is a stable, colorless, crystalline substance. It is soluble in chloroform and dichloromethane, less soluble in benzene and methanol, and sparingly soluble in diethyl ether and hexane. Notably, while the molecular ion of **1** is weak in an EI-MS spectrum, the base peak is a fragment peak corresponding to the mass of tris(2-pyridyl)methyl cation. This observation suggests a considerable stability of tris(2-pyridyl)methyl cation in spite of the electron-withdrawing property of 2-pyridyl group.

^{1}H and ^{13}C NMR spectra of (2-pyridyl)methanes (Table 2 for the data) are consistent with the tetrapyridyl structure of **1**. All the 2-pyridyl groups of **1** are observed to be equivalent at 30°C, and ^{1}H NMR spectrum showed no broadening of the signals down to −50°C. Thus, 2-pyridyl groups are fast rotating around room temperature. Significantly large changes in the chemical shifts are observed for the inner protons (H-3) and carbons (C-α, C-2 and C-3) which move down-field as the number of 2-pyridyl group increases. This trend is in contrast with rather high-field shift of the *ortho*-protons in tetraphenylmethane.[6]

The structure of **1** was established by X-ray analysis (Fig. 1).[7] 2-Pyridyl groups orient so that the sp^2 nitrogen atoms locate most apart each other. In this conformation, H-3 and the unshared electrons on the nitrogen atoms are situated rather close, which might explain the down-field shift of H-3. The bond-lengths between C-α

Table 1. The synthesis of tetrakis(2-pyridyl)methane **1**[a]

Entry	Solvent[a]	Products (%)		
		1	(2-Py)$_3$CH **5**	(2-Py)$_3$COH
1	THF	1	80	0
2	Toluene	6	89	4
3	Xylene	28	65	6
4	Mesitylene	52	47	0

[a] All the reactions were performed by refluxing the reaction mixture for 24 h under nitrogen atmosphere, and the products were isolated by chromatography on alumina.

Table 2. ^{1}H and ^{13}C NMR chemical shifts[a] of 2-pyridylmethanes

Compound	^{1}H, δ (ppm)					^{13}C, δ (ppm)					
	C-α	H-3	H-4	H-5	H-6	C-α	C-2	C-3	C-4	C-5	C-6
2-MePy	2.55	7.14	7.55	7.08	8.49	24.40	158.10	122.97	135.90	120.43	148.90
$(2\text{-Py})_2CH_2$	4.33	7.24	7.56	7.08	8.53	47.18	159.14	123.34	136.28	121.22	149.12
$(2\text{-Py})_3CH$	6.00	7.32	7.60	7.12	8.57	64.02	160.84	123.94	136.25	121.50	149.20
$(2\text{-Py})_4C$	–	7.49	7.60	7.08	8.53	72.36	163.96	125.81	135.62	120.81	148.00

[a] In $CDCl_3$ at 270 or 400 MHz at 30°C.

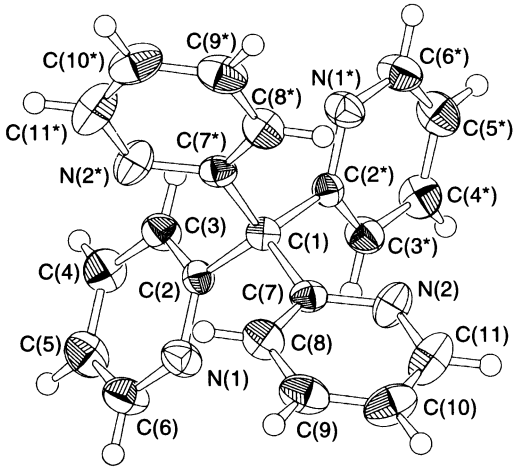


Figure 1. ORTEP drawing of **1** along *b* axis (50% probability). Selected bond lengths (Å) and angles (°): C(1)–C(2) 1.547(4), C(1)–C(7) 1.538(4), N(1)–C(2) 1.324(4), N(1)–C(6) 1.345(4), C(2)–C(3) 1.396(4), C(3)–C(4) 1.370(5), C(4)–C(5) 1.377(5), C(5)–C(6) 1.365(5); C(2)–C(1)–C(2*) 106.6(4), C(2)–C(1)–C(7) 111.7(2), C(2)–C(1)–C(7*) 110.3(2), C(7)–C(1)–C(7*) 106.3(4), N(1)–C(2)–C(3) 121.9(3), C(2)–C(3)–C(4) 119.7(3), C(3)–C(4)–C(5) 118.3(5), C(4)–C(5)–C(6) 118.8(3), C(5)–C(6)–N(1) 123.6(3), C(2)–N(1)–C(6) 117.6(3).

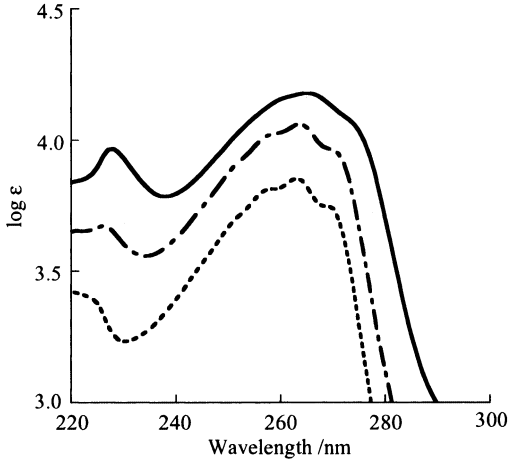


Figure 2. UV–vis spectra of **1** (—), $(2\text{-Py})_3CH$ (–·–), and $(2\text{-Py})_2CH_2$ (····) in CH_2Cl_2.

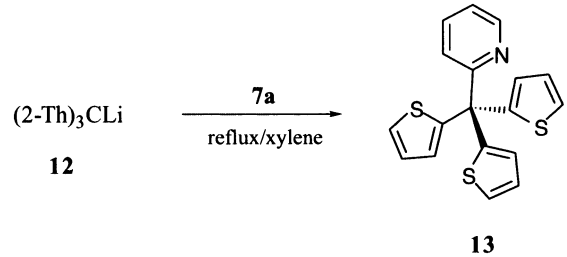
and *ipso*-carbons (1.543 Å in average) are slightly shorter than those of tetraphenylmethane (1.550 Å in average[8]), suggesting a smaller steric congestion around C-α.

Absorption spectrum of **1** is similar to those of $(2\text{-Py})_3CH$ and $(2\text{-Py})_2CH_2$,[5,9] exhibiting only slight red-shift of the absorption maxima and absorption edge (Fig. 2). Therefore, intramolecular interaction between the pyridyl groups, such as homoconjugation, is not evident. The high symmetry of the molecule may be a reason for the absence of clear interaction.[10]

Upon dissolution in trifluoroacetic acid, **1** forms tetrakis(pyridinium)methane **10** whose ^{1}H NMR spectrum shows large down-field shifts similar to those of the parent pyridinium ion[11], except that the inner protons (H-3) move down-field only slightly ($\Delta\delta$ 0.07).[12] Oxidation of **1** with excess peracetic acid afforded tetrakis(*N*-oxide) **11** in 46% yield as a crystalline substance.[13] Its NMR spectra also show a high symmetry of the molecule at ambient temperature.

The nucleophilic aromatic substitution here employed for the synthesis of **1** should be applicable to the synthesis of other tetrakis(heteroaryl)methanes. Actually, the reaction of tris(2-thienyl)methyl anion **12**[14] with 2-chloropyridine (5 equiv.) in refluxing xylene (24 h) afforded 2-pyridyl-tris(2-thienyl)methane **13**[15,16] in 8% yield (Scheme 2).

In summary, tetrakis(2-pyridyl)methane **1** has been first synthesized as a stable compound in moderate yield. Further studies on **1** including complexation ability and attempts to synthesize other tetrapyridylmethanes, in particular, tetrakis(4-pyridyl)methane, are in progress.



Scheme 2.

Acknowledgements

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4. Physical data for **9**: colorless crystals; mp 184–185°C; EI-MS *m*/*z* (rel. intensity) 492 (M^+, 13.8), 491 (M^+–H, 24.5), 414 (M^+–C_5H_4N, 100), 246 (M^+–$(2\text{-Py})_3C$, 23.4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (s, 1H), 7.08–7.13 (m, 5H), 7.25 (d, J=7.9 Hz, 1H), 7.29 (dt, J=8.1, 1.0 Hz, 3H), 7.34 (dt, J=7.9, 1.0 Hz, 2H), 7.58 (td, J=7.8, 1.9 Hz, 3H), 7.59 (td, J=7.7, 1.9 Hz, 2H), 7.65 (dd, J=8.3, 2.5 Hz, 1H), 8.44 (dd, J=2.5, 0.7 Hz, 1H), 8.53–8.56 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.93, 68.61, 121.42, 121.70, 122.89, 124.36, 125.69, 128.42, 136.12, 136.50, 139.20, 148.65, 149.46, 152.02, 158.16, 161.31, 163.90. The NMR data indicate the presence of three kinds of pyridyl groups in 3:2:1 ratio (one of them being disubstituted at 2,5-positions), two aliphatic carbons, and one aliphatic proton whose chemical shift is similar to that of $(2\text{-Py})_3CH$.
5. Physical data for **1**: colorless needles; mp 259–260°C; EI-MS *m*/*z* (rel intensity) 324 (M^+, 2.0), 323 (M^+–H, 4.2), 246 (M^+–C_5H_4N, 100), 168 (M^+–$2(C_5H_4N)$, 4.7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (ddd, J=7.7, 5.0, 1.0 Hz, 4H), 7.49 (dt, J=7.7, 1.0 Hz, 4H), 7.60 (td, J=7.7, 1.9 Hz, 4H), 8.53 (ddd, J=5.0, 1.9, 1.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.36 (C-α), 120.81 (C-5), 125.81 (C-3), 135.62 (C-4), 148.00 (C-6), 163.96 (C-1); UV–vis (CH_2Cl_2) λ_{max}/nm (ε) 228 (9200), 260sh (14300), 265 (15100), 273sh (11900). Anal calcd for $C_{21}H_{16}N_4$: C, 77.76%; H, 4.97%; N, 17.27%. Found: C, 77.86%; H, 4.90%; N, 17.14%.
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7. Crystallographic data for **1**: $C_{21}H_{16}N_4$, FW=324.38, monoclinic, space group *C*2/*c* (#15), a=16.147(4), b=7.190(3), c=14.950(3) Å, β=112.60(2)°, Z=4, V=1602.5(9) Å^3. The measurement was performed with Rigaku AFC5R diffractometer; radiation MoKα (λ=0.71069 Å); of a total of 2092 reflections collected, 1846 were unique (R_{int}=0.098) for 2θ<55.0°. The structure was solved by the direct method using SHELXS-86 with a GOF 0.99. Final residuals are R=0.182, R_w=0.141, and R_1=0.050. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 203311.
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9. UV–vis (CH_2Cl_2) data: λ_{max}/nm (ε) 220 (2600), 257sh (6400), 263 (7100), 269sh (5600) for bis(2-pyridyl)-methane; 226 (4700), 258sh (10500), 263 (11500), 270sh (9200) for tris(2-pyridyl)methane **5**.
10. Reduction of the symmetry of **1** by introduction of substituents, in particular of push–pull nature, would make the interaction more evident as the case in tetraphenylmethane derivatives.[17]
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12. NMR data of **1** in trifluoroacetic acid-d_4, that is **10**: ^{1}H NMR (270 MHz) δ 7.56 (dt, J=8.1, 1.1 Hz, H-3, 4H), 8.00 (ddd, J=7.8, 5.5, 1.1 Hz, H-5, 4H), 8.37 (td, J=8.0, 1.7 Hz, H-4, 4H), 9.06 (ddd, J=5.5, 1.7, 0.9 Hz, H-6, 4H); ^{13}C NMR (67.8 MHz) δ 57.54 (C-α), 129.12 (C-5 or C-3), 130.33 (C-3 or C-5), 146.94 (C-6 or C-4), 147.08 (C-4 or C-6), 156.80 (C-2).
13. Physical data for **11**: colorless crystals; mp 294°C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.97 (dd, J=8.2, 1.9 Hz, H-3, 4H), 7.25 (td, J=7.9, 1.3 Hz, H-4, 4H), 7.34 (td, J=7.0, 1.9 Hz, H-5, 4H), 8.02 (dd, J=6.4, 1.3 Hz, H-6, 4H); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 59.63, 123.58, 124.67, 130.61, 139.01, 144.29.
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15. Physical data for **13**: colorless crystals; mp 153–154°C; EI-MS *m*/*z* (rel intensity) 339 (M^+, 100), 261 (M^+–C_5H_4N, 77); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.83 (dd, J=3.6, 1.2 Hz, Th-H-3, 3H), 6.95 (dd, J=5.3, 3.6 Hz, Th-H-4, 3H), 7.15 (dt, J=8.1, 1.0 Hz, Py-H-3, 1H), 7.22 (ddd, J=7.5, 4.7, 1.1 Hz, Py-H-5, 1H), 7.26 (dd, J=5.3, 1.2 Hz, Th-H-5, 3H), 7.62 (td, J=7.8, 1.9 Hz, Py-H-4, 1H), 8.72 (ddd, J=4.7, 1.9, 0.9 Hz, Py-H-6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.91, 122.12, 122.53, 125.64, 136.10, 148.07, 151.20, 164.12; UV–vis (CH_2Cl_2) λ_{max}/nm (ε) 231sh (29000), 239 (32600).
16. The yield of **13** was not improved in mesitylene probably because of poorer thermal stability of **12** than **6**.
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