Pergamon

Tetrahedron Vol. 50, No. 41, pp. 11893-11902, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00777-2

A Convenient Synthetic Route to *bis*-Heteroaromatic and *bis*-Heterocyclic Compounds Promoted by Liganded Nickel Complex Reducing Agents.

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***Abstract** : A number of nitrogen, sulfur or oxygen containing bis-heteroaromatic or bis-heterocyclic derivatives have been synthesized in good to excellent yields by homo-coupling of the corresponding halogenated compounds in the presence of liganded (triphenylphosphine or 2,2'-bipyridine) nickel Complex Reducing Agents in THF or DME at 63°C.*

INTRODUCTION

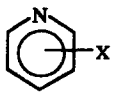
Aggregative activation (AA) theory describes the possible consequences of mixing ionic reagents.[1] Thus, Super Bases [2] which Complex Bases[3] are particular examples stem from the mixing of two or more bases. On an other hand metal containing Complex Reducing Agents noted MCRA (*in situ* prepared mixtures of sodium hydride, sodium alkoxide and metal salt)[4] are also directly related to the AA theory.[3] MCRA are versatile easily prepared and unexpensive reagents able to perform selective reductions,[5] desulfurizations[6] as well as carbonylations[7] and coupling of organic halides.[8]

Examination of the literature shows that *bis*-heterocyclic derivatives are interesting compounds with numerous potential fields of applications such as electrical or electronical materials,[9] biological compounds[10] or chelating agents and organic ligands.[11] Two main syntheses of *bis*-heteroaromatic compounds emerge from the various preparations described. One requires the condensation of heteroorganometallic reagents with heteroaryl halides.[12] The other consists in the direct coupling of heteroaryl halides.[13,14] Of course the second one is much more attractive since it is less expensive and avoids the preparation and handling of organometallics. However it appears that the reactions described suffer from a number of limitations[12-14] and that new complementary methods are needed in order to extend the application fields of the direct coupling of heterocyclic halides.

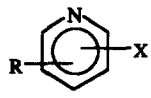
In this context we report in the present paper the results obtained with liganded nickel containing Complex Reducing Agents noted NiCRAL, L representing triphenylphosphine or 2,2'-bipyridine.[4]

RESULTS AND DISCUSSION

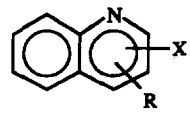
Homo-Coupling of Nitrogen Containing Heteroaromatic Halides. We first examined the homo-coupling of nitrogen containing halogenated heteroaromatic compounds (Scheme 1 and Table 1).



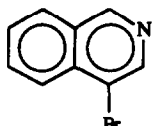
1a X = 2-Br **1e** X = 3-Cl
1b X = 3-Br **1f** X = 4-Cl
1c X = 4-Br **1g** X = 2-F
1d X = 2-Cl



2a X = 2-Br ; R = 6-Me
2b X = 2-Cl ; R = 6-MeO
2c X = 2-Cl ; R = 5-CF_3
2d X = 3-Cl ; R = 2-NH_2



3a X = 2-Cl ; R = H
3b X = 3-Br ; R = H
3c X = 3-Cl ; R = 2-Me



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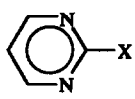
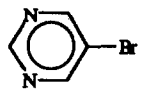


5a X = Br
5b X = Cl



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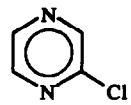

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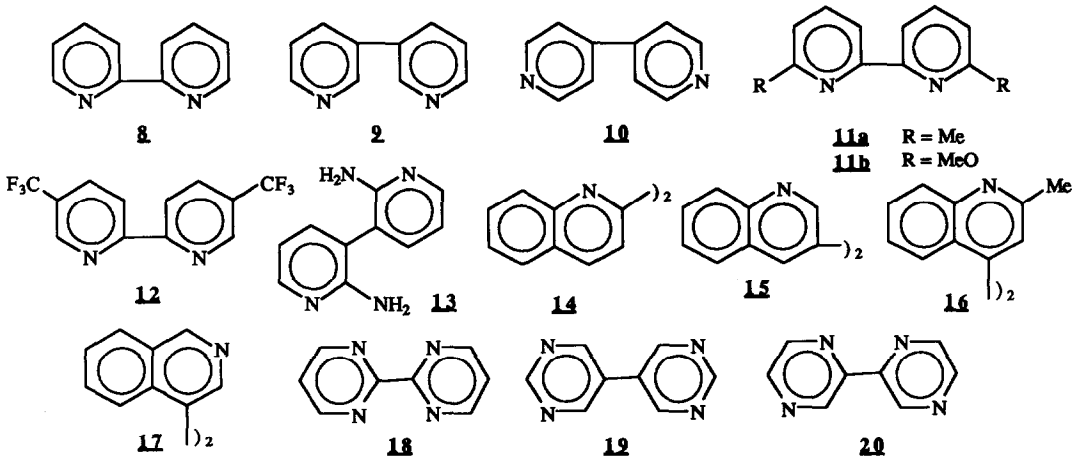
Scheme 1

From unreported experiments (performed during the beginning of this study) it appeared that *t*-BuONa and *t*-AmONa were the best activating agents in DME and THF respectively. As previously observed with aryl halides polar aprotic solvents considerably favored reductions, the main side reactions of the coupling with NiCRA's.[8] On an other hand, the most appropriated ligand to perform these reactions was triphenyl phosphine which is very easily separated from the coupling product. Only in one case (run 10) 2,2'-bipyridine appeared as a better ligand, however its separation from the product was easy.

From a more systematic study performed with halopyridines **1** and **2** (runs 1 to 11) it appeared that broadly speaking and for a given halide the reactivity of the substrates follows the trend of their aptitude to nucleophilic substitution. However the ratio reduction/coupling (the only main by-product came from reduction) increases with the reactivity toward nucleophiles as well as with the temperature and the reaction time. The best conditions were given in the Table 1. Another way to decrease the side reduction (the only observed side-reaction) should be in lowering the NaH content of CRA's.[8d] However in the pyridine as well in the quinoline **3** or isoquinoline **4** series a decrease of NaH led to much less efficient coupling with no improvment of the selectivity. On the contrary with the very reactive halopyrimidines **5** and **6** and pyrazines **7** the only way to obtain coupling product was the use of NiCRAL (2.2.1.4) (procedure C).

In these conditions, with a few exceptions, coupling products (Scheme 2) were obtained in good to excellent yields. NiCRAL then appeared as good canditates for homocoupling of nitrogen containing heterocyclic compounds. For example, it was to be noticed that NiCRAL (yield = 50%) appeared better than Pd/Zn/PPh_3 system (yield = 32%) toward the coupling of 2-chloro-5-(trifluoromethyl) pyridine **2c**.[14]



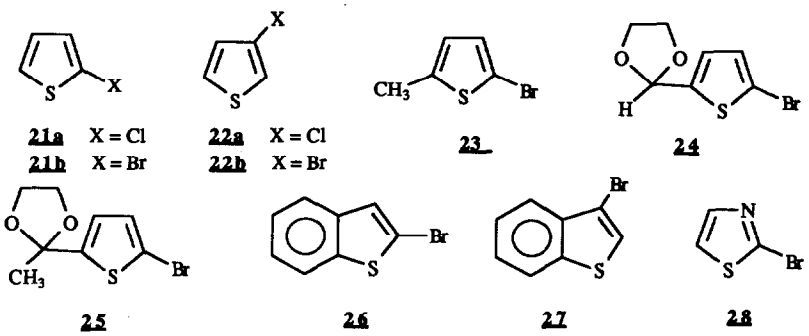
Scheme 2

Table 1. Homo-Coupling of Nitrogen Containing Heteroaromatic Halides.[a]

Run	Substrate	Procedure[b]	Temperature °C	Time (h)	Product	Yield %[c]
1	**1a**	A	45	2	**8**	70
2	**1b**	A	45	3	**9**	78
3	**1c**	A	45	3	**10**	78
4	**1d**	A	45	3.5	**8**	66
5	**1e**	A	65	5	**9**	90
6	**1f**	A	45	2	**10**	86
7	**1g**	A	65	4	**8**	51
8	**2a**	A	45	2	**11a**	73
9	**2b**	A	45	2.5	**11b**	80
10	**2c**	B	25	136	**12**	50 (57)
11	**2d**	A	65	17	**13**	40 (44)
12	**3a**	A	45	3	**14**	70
13	**3b**	A	45	1.5	**15**	72
14	**3c**	A	45	3.5	**16**	71
15	**4**	A	45	4	**17**	53
16	**5a**	C	25	17	**18**	30 (43)
17	**5b**	C	25	17	**18**	40 (44)
18	**6**	C	25	17	**19**	53
19	**7**	C	45	10	**20**	43 (48)

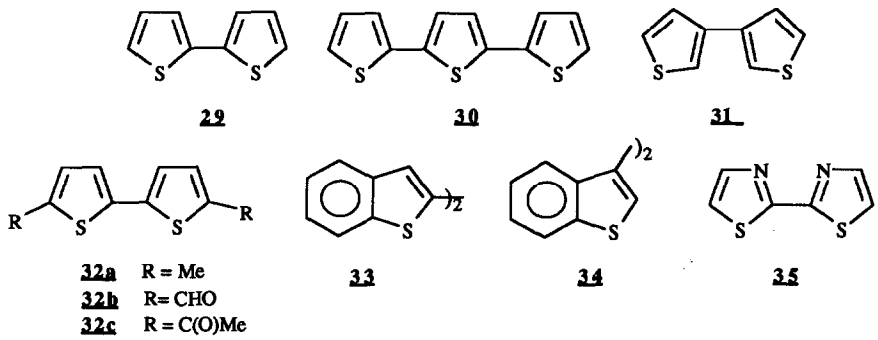
a) Reaction performed on a 10 mmoles scale. b) Procedure A: *t*-BuONa-NiCRA-PPh_3 (4.2.1.4) in 60 ml DME; Procedure B: *t*-AmONa-NiCRA-bpy (3.2.1.2) in 60 ml THF; Procedure C: *t*-BuONa-NiCRA-PPh_3 (2.2.1.4) in 60 ml DME. c) Isolated yield by flash chromatography. In parenthesis, isolated yield based on converted starting material.

Homo-coupling of sulfur or oxygen heterocyclic halides. We then turned toward the coupling of sulfur containing heterocycles (Scheme 3). The obtained results were reported in Table 2 (runs 1 to 10).



Scheme 3

It first appeared that in general 2,2'-bipyridine was the more appropriated ligand to perform these coupling reactions. On an other hand, it is well known that sulfur easily complex to nickel which, in turn, is a very efficient desulfurizing reagents.[6] In fact we previously published very efficient and chemioselective desulfurizations of (benzo)thiophene derivatives with NiCRA's.[6b] Under the conditions used in the present work no such reaction was observed. This result must be attributed to the presence of the ligands 2,2'-bipyridine (Table 2, runs 1 to 9) and triphenylphosphine (Table 2, run 10). Indeed from the Eisch[15] as well as our own's works[6] it seems likely that the first step of desulfurizations is a single electron transfer (SET). NiCRAL's are much weaker reducing agents than NiCRA's[5b] a property which parallel the SET ability. Moreover the ligand of NiCRAL empedes the sulfur to efficiently complex Ni. Thus it is not surprising that desulfurizations were not observed. In fact couplings took place in good to excellent yields whatever the nature of the halide, the main side reaction being, as usual, reduction.



Scheme 4

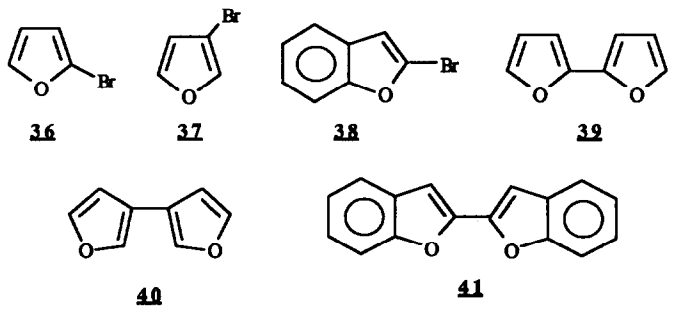
Surprisingly we observed with 2-halothiophenes **21** the formation, in appreciable amount (~25 %) of 2,2':5',2"-terthiophene **30**. Such trimerization has already been observed by others[16] however for the present time no clear explanation of this strange reaction has been done.

Table 2. Homo-coupling of sulfur and oxygen containing heterocyclic halides.[a]

Run	Substrate	Procedure[b]	Temperature °C	Time (h)	Product	Yield %[c]
1	**21a**	D	25	17	**29**	60[d]
2	**21b**	D	25	1	**29**	70[e]
3	**22a**	D	25	18	**31**	52 (66)
4	**22b**	D	25	3	**31**	60
5	**23**	D	25	1.5	**32a**	73
6	**24**	D	45	17	**32b**	53
7	**25**	D	25	17	**32c**	67
8	**26**	D	25	1	**33**	82
9	**27**	D	25	17.5	**34**	70
10	**28**	E	45	1	**35**	62
11	**36**	F	25	1	**39**	10
12	**37**	F	25	17.5	**40**	42
13	**38**	F	25	1	**41**	70

a) Reaction performed on a 10 mmoles scale. b) Procedure D: *t*-AmONa-NiCRA-bpy (4.2.1.2) in 60 ml THF; Procedure E: *t*-BuONa-NiCRA-PPh_3 (4.2.1.4) in 60 ml benzene; Procedure F: t-BuONa-NiCRA-bpy (2.2.1.2) in 60 ml THF. c) Isolated yield by flash chromatography. In parenthesis, isolated yield based on converted starting material. d) 24 % of 2,2':5',2"-terthiophene **30** was also isolated. e) 25 % of 2,2':5',2"-terthiophene **30** was also isolated.

Finally a few oxygen containing heterocycles were examined (Scheme 5, Table 2, runs 11 to 13).



36 **37** **38** **39** **40** **41**

Scheme 5

In spite of our efforts to perform the coupling of 2-bromofurane **36**, the results obtained were disappointing the main reaction observed being the reduction. We have no explanation for this lack of success all the more because 3-bromofurane **37** and above all 2-bromobenzofurane **38** coupled in good to excellent yields.

CONCLUSION

NiCRAL's are good reagents to couple nitrogen, sulfur or oxygen containing heterocyclic halides, a result which nicely complete the results obtained with aryl halides. Works are in progress in order to perform cross couplings.

EXPERIMENTAL

General. Melting points were determined with a Tottoli capillary melting point apparatus and were uncorrected. Infrared spectra (ir) were recorded on a Perkin-Elmer 841 spectrophotometer. NMR spectra were taken on a Jeol PMX 60SI or a Bruker AM 400. Chemical shift values are reported relative to tetramethylsilane in the appropriate solvent. Nominal mass spectra were recorded on a Hewlett-Packard 5890 Series II mass spectrometer. GC analysis were achieved with a Girdel 300 chromatograph equipped with a 6 ft x 0.25 in column of 10% SE 30 on chromosorb WAW. All reactions were conducted under a nitrogen atmosphere (quality R, Airgaz). Flash chromatography was carried out on Merck silica gel (230- 400 mesh). THF was distilled from a benzophenone-sodium adduct and stored over sodium wires. DME and benzene were distilled from sodium and stored over sodium wires. The absence of peroxides was checked before each run. *tertio*-Amyl alcohol or *tertio*-butyl alcohol (Aldrich) was distilled from sodium. Nickel acetate (Fluka) was recristallized before use from hexane. Sodium hydride (Fluka) was used after three washings with the reaction solvent under nitrogen. Each batch of sodium hydride was titrated by standard techniques[17] before use.

Substrates. 2-Bromopyridine (**1a**), 3-bromopyridine (**1b**), 4-bromopyridine (**1c**), 2-chloropyridine (**1d**), 3-chloropyridine (**1e**), 4-chloropyridine (**1g**), 2-fluoropyridine (**1g**), 2-chloro-6-methoxypyridine (**2b**), 2-chloro-5-(trifluoromethyl)pyridine (**2c**), 3-chloro-2-amino-pyridine (**2d**), 2-chloroquinoline (**3a**), 3-bromoquinoline (**3b**), 4-chloro-2-methylquinoline (**3c**), 3-bromoisoquinoline (**4**), 2-bromopyrimidine(**5a**), 2-chloropyrimidine (**5b**), 5-bromopyrimidine (**6**), 2-chloropyrazine (**7**), 2-chlorothiophene (**21a**), 2-bromothiophene (**21b**), 3-chlorothiophene (**22a**), 3-bromothiophene (**22b**), 2-bromo-5-methylthiophene (**23**), 2-bromothiazine (**28**), 3-bromofurane (**36**) were obtained from commercial sources (Aldrich, Janssen, Lancaster, TCI).

2-Bromo-6-methylpyridine (**2a**) was prepared exactly as described by Adams and Miyano[18] (yield: 78%; bp: 102-103°C / 25 mbar). (5'-Bromo)-2-thienyl)-1,3-dioxolane (**24**) was prepared from 5-bromothiophene-2-carbo-aldehyde ethylene glycol and p-toluene sulfonic acid in benzene according to the method of Feringa and Brandsma[19] (yield: 60%; bp: 87-88°C / 1 mbar). (5'-Bromo)-2-thienyl)- 2-methyl-1,3-dioxolane (**25**) was prepared from 5-bromo-2-acetylthiophene, ethylene glycol and *p*-toluene sulfonic acid in benzene according to the method of Smith[20] (yield: 74%; mp: 80-81°C). 2-Bromobenzothiophene (**26**) was prepared exactly as described by Coderc[21] (yield: 70% ; mp: 41-42°C). 3-Bromobenzothiophene (**27**) was prepared from benzothiophene, N-bromo succinimide and APTS in benzene at reflux during 16 h according to the procedure of Prugh[22] (yield: 52%; bp: 95°C / 2 mbar). 2-Bromofurane (**37**) was prepared exactly as described by Prugh[22] (yield:30%; bp: 50°C / 240 mbar). 2-Bromobenzofurane (**38**) was prepared exactly as described by Coderc[21] (yield: 50%; bp: 221-223°C).

General procedures

Procedure A. ***t-BuONa-NiCRA-PPh$_3$ (4.2.1.4), DME***: *t*-BuOH (20 mmol) in 10 ml of DME was added dropwise to a suspension of NaH (60 mmol), $Ni(OAc)_2$ (10 mmol) and triphenylphosphine (40 mmol) in DME (30 ml) at 65°C. After 2 h of stirring, the reagent was ready for use and the substrate could be added in DME (20 ml) at the desired temperature.

Procedure B. ***t-AmONa-NiCRA-bpy (3.2.1.2), THF***: *t*-AmOH (20 mmol) in 10 ml of THF was added dropwise to a suspension of NaH (50 mmol), $Ni(OAc)_2$ (10 mmol) and 2,2'-bipyridine (20 mmol) in refluxing THF (30 ml). After 2 h of stirring, the reagent was ready for use and the substrate could be added in THF (10 ml) at the desired temperature.

Procedure C. ***t-BuONa-NiCRA-PPh$_3$ (2.2.1.4), DME***: Procedure A was employed using only 40 mmol of NaH in place of 60 mmol.

Procedure D. ***t-AmONa-NiCRA-bpy (4.2.1.2), THF***: Procedure B was employed using 60 mmol of NaH in place of 50 mmol.

Procedure E. ***t-BuONa-NiCRA-PPh$_3$ (4.2.1.4), benzene***: Procedure A was employed using benzene as solvent in place of DME.

Procedure F. ***t-AmONa-NiCRA-bpy (2.2.1.2), THF***: Procedure B was employed using 40 mmol of NaH in place of 50 mmol.

The reactions were monitored by GC analysis of small aliquats. The internal standard was hydrocarbon (C_8-C_{16}). After completion of the reaction, the excess of hydride was carefully destroyed by dropwise addition of EtOH at 25°C until hydrogen evolution ceased. After addition of water, the organic phase was extracted into diethyl ether and dried over $MgSO_4$. After removal of the solvents, products were separated by flash chromatography using an appropriate EtOAc/hexane mixture as eluent. Note that volatile products must be isolated by distillation instead of chromatography.

Products. 2,2'-Bipyridine (**8**), 4,4'-bipyridine (**10**) and 2,2'-Bipyrimidine (**18**) 5,5'-Bipyrimidine (**19**) were identical in every respect with commercial samples.

3,3'-Bipyridine (**9**) : mp 43-45°C (lit.[23], 44°C); ^{1}H NMR (CCl_4) δ: 7.4 (m, 1H), 7.9 (dt, 1H), 8.6 (dd, 1H), 8.9 (dd, 1H).

6,6'-Dimethyl-2,2'-bipyridine (**11a**) : mp 90°C (lit.[24], 88-89°C). Spectral properties are described in the literature.

6,6'-Dimethoxy-2,2'-bipyridine (**11b**) : mp 118°C (lit.[25], 119°C). ^{1}H NMR (CCl_4) δ: 4.0 (s, 6H), 6.8 (d, J = 8 Hz, 2H), 7.5-8.1 (m, 4H).

5,5'-Bi-(trifluoromethyl)-2,2'-bipyridine (**12**) : mp 123°C (lit.[14], 124-126°C). Spectral properties are described in the literature.

2,2'-Diamino-3,3'-bipyridine (**13**) : mp 132°C (lit.[26], 134°C); ^{1}H NMR ($CDCl_3$) δ: 3.6 (s, 2H), 6.9 (d, 2H), 87.7 (t, 1H); ^{13}C NMR ($CDCl_3$) δ: 121.3, 123.6, 137.2, 139.6, 142.6.

2,2'-Biquinoline (**14**) : mp 197°C (lit.[27], 196-198°C); ^{1}H NMR ($CDCl_3$) δ: 7.4- 8.0(m, 3H), 8.2 (d, 2H), 8.9 (d, 1H).

3,3'-Biquinoline (**15**) : mp 270°C (lit.[28], 271°C); ^{1}H NMR ($CDCl_3$) δ: 7.4 (m, 1H), 7.2-7.9 (m, 3H), 8.1 (m, 2H), 8.9 (d, 1H).

2,2'-Dimethyl-4,4'-biquinoline (**16**) : mp 298°C (lit.[29], 298°C); ^{1}H NMR ($CDCl_3$) δ: 2.8 (s, 6H), 7.2-7.4 (m, 6H), 7.5-7.9 (m, 2H), 8.1-8.4 (dd, 2H); ^{13}C NMR ($CDCl_3$) δ: 25.3, 122.5, 125.1, 125.5, 126.0, 129.0, 129.6, 144.5, 147.9, 158.4.

4,4'-Bisisoquinoline (**17**) : mp 133°C (lit.[30], 134°C). Spectral properties are described in the literature.

2,2'-Bipyrazine (**20**) : mp 162-165°C (lit.[31], 164°C). ^{1}H NMR ($CDCl_3$) δ: 8.7 (s, 2H), 9.6 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 143.4, 143.7, 145.2, 149.3.

2,2'-Bithiophene (**29**) : mp 33°C (lit.[32], 33°C). Spectral properties are described in the literature.

2,2':5',2"-Terthiophene (**30**) : mp 93-94°C (lit.[33], 93-94°C); ^{13}C NMR ($CDCl_3$) δ: 123.6, 124.2, 127.8, 136.1, 137.1.

3,3'-Bithiophene (**31**) : mp 130°C (lit.[34], 130°C); ^{1}H NMR ($CDCl_3$) δ: 7.3 (s, 2H), 7.4 (s, 1H); ^{13}C NMR($CDCl_3$) δ: 15.2, 122.8, 125.7, 135.4, 138.4.

5,5'-Dimethyl-2,2'-bithiophene (**32a**) : mp 68°C (lit.[35], 68°C). Spectral properties are described in the literature.

5,5'-Biformyl-2,2'-bithiophene (**32b**) : mp 218°C (lit.[36], 218-219°C); ^{1}H NMR ($CDCl_3$) δ: 7.4 (dd, 2H, J = 12 Hz), 9.7 (s, 1H); CIMS: 223 (M+H).

5,5'-Biacetyl-2,2'-bithiophene (**32c**) : mp 196°C (lit.[36], 195-197°C); ^{1}H NMR ($CDCl_3$) δ: 1.7 (s, 3H), 2.5 (s, 3H), 3.9 (s, 4H), 7.1-7.8 (m, 4H); CIMS: 295 (M+H).

2,2'-Bibenzothiophene (**33**): mp 233-235°C (lit.[37], 233-235°C). ^{1}H NMR ($CDCl_3$) δ: 7.1-7.4 (m, 3H), 7.6-7.9 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 122.7, 123.1, 124.2, 124.5, 131.3, 138.5, 140.1; CIMS: 267 (M+H).

3,3'-Bibenzothiophene (**34**) : mp 254°C (lit.[37],258-259°C) Spectral properties are described in the literature.

2,2'-Bithiazine (**35**) : mp 102°C (lit.[38], 103°C). ^{1}H NMR ($CDCl_3$) δ: 7.3 (d, 1H), 7.8 (d, 1H); ^{13}C NMR ($CDCl_3$) δ: 77.2, 100.1, 117.8.

2,2'-Bifurane (**39**) : mp 39°C (lit.[39], 40°C). ^{1}H NMR ($CDCl_3$) δ: 6.3 (d, 2H), 7.4 (d, 1H); CIMS: 135 (M+H). Volatile compound.

3,3'-Bifurane (**40**) : mp 44-45°C (lit.[40], 45.5-46°C). ^{1}H NMR ($CDCl_3$) δ: 6.3 (s, 1H), 7.4 (s, 1H), 7.5 (s, 1H).

2,2'-Bibenzofurane (**41**) : mp 176°C (lit.[41], 175-177°C). ^{1}H NMR ($CDCl_3$) δ: 7.0-7.6 (m); ms: 235 (M+H).

Acknowledgements: We thank the referees from help and comments.

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4 In the present paper we have adopted the following convention : a NiCRAL prepared from NaH, *t*-AmONa, nickel acetate, and 2,2'-bipyridine or triphenylphosphine will be abbreviated NiCRAL (x/y/z/t),

where the molar ratio NaH/*t*-AmONa/$Ni(OAc)_2$/2,2'-bipyridine or triphenylphosphine (in that order) is equal to x/y/z/t. It must be noted that during the preparation of NiCRAL's 2 equivalents of NaH are needed in order to reduce 1 equivalent of Ni^{2+} species. So for example and according to our definitions a NiCRAL (2.2.1.t) contains no remaining hydride equivalent at the end of its preparation. On the contrary NiCRAL's (3.2.1.t) and (4.2.1.t) contain respectively one and two hydride equivalents.

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(*Received in Belgium* 25 *May* 1994; *accepted* 25 *June* 1994)