Tetrahedron Vol. 41, No. 10, pp. 1919 to 1929, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

SYNTHESIS AND ^{13}C NMR CHARACTERIZATION OF SOME π-EXCESSIVE HETEROPOLYAROMATIC COMPOUNDS[a)]

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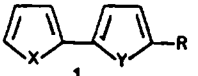
(*Received in UK* 12 *February* 1985)

Abstract - Several π-excessive heteropolyaromatic compounds, which contain furan and thiophen ring and are possible antifungal agents, have been synthesized in good yields according to two general methods. The first method has been used to prepare compounds possessing thiophens linked by their 2- and 5-positions, such as the ter-aryls 2b, 2d and 2a. Two precursors of these compounds have been obtained either by the Glaser reaction, or using a novel Pd-mediated reaction. The second method, which consists of the Ni-or Pd-catalyzed heteroarylation of heteroarene halides via cross-coupling with heteroaryl Grignard reagents or zinc halides, has been used to prepare the bi-aryls 1a-e, which contain two heteroaromatic units, and the ter-aryl 2c. Compound 1e has been also prepared starting from 2-(2-thienyl)furan (1c) by selective lithiation, followed by bromination.
The ^{13}C NMR signals of 1a-e and 2a-d have been assigned on the basis of the literature data and by relaxation measurements. Relaxation data have been also used to obtain qualitative informations on the conformational equilibria of the bi-aryls 1a, 1c and the ter-aryls 2a-d.

In connection with our studies on the synthesis of biologically active naturally-occurring compounds and derivatives[1], we were interested in developing general and convenient methods for the synthesis of functional derivatives of 2,2'-bithiophen (1a), 2,2':5',2"-terthiophen (2a) and of structural derivatives of these compounds containing either furan or thiophen rings. It has been reported that many 2,2'-bithienyl and 2,2':5',2"-terthienyl derivatives display interesting biological properties[2-10]. Moreover, the chemistry of such π-excessive heteropolyaromatic compounds is an area of heterocyclic chemistry which remains to be explored in detail. In fact, apart from Bohlmann's pioneering work on some naturally-occurring 2,2'-bithienyl and 2,2':5',2"-terthienyl derivatives[11] and some recent syntheses of few 2,2'- and 2,3'-bithienyl compounds[1e,12] and α-thiophen oligomers[13,14], there has been little development. In particular there is little information in the literature on open chain π-excessive heteropolyaromatic compounds containing different heteroarene components[15-17], and much less on their reactivity and functionalization[18]. This is apparently due to the lack of efficient preparative methods.

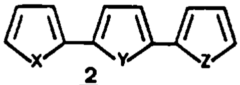
We describe herein two efficient methods for the synthesis of π-excessive heteropolyaromatic compounds of general formula 1 and 2.

(a) Research work supported by CNR, Italy, Special Grant I.P.R.A. - Sub-project 1- Paper N. 386 - and by Ministero della Pubblica Istruzione.



1

a X=S;Y=S;R=H
b X=S;Y=S;R=Br
c X=S;Y=O;R=H
d X=S;Y=O;R=Br
e X=O;Y=S;R=Br



2

a X=Y=Z=S
b X=Y=S;Z=O
c X=Z=S;Y=O
d X=Z=O;Y=S

The first method has been used to prepare the ter-aryls 2a,2b and 2d, which possess thiophens linked by their 2- and 5- positions and are characterized by the presence of three heteroaromatic units.The second method which is more general allows the straightforward synthesis of 1a–e and 2c, which contain two or three heteroaromatic units,respectively.Compounds 1d,2b,2c and 2d have not been previously described.The bi-aryls 1b,1c and 1e have been previously prepared by reaction sequences affording low overall yields[16,17,18,20].

A different approach for the preparation of 1d and 1e,which is based on the selective α-lithiation of 1c, is also reported and discussed.

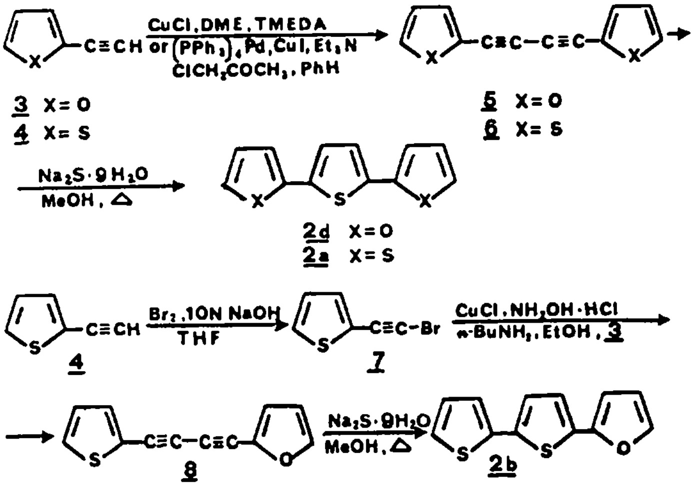
Finally,the paper deals with the interpretation of the ^{13}C NMR spectra of 1a–e and 2a–d on the basis either of the chemical shift data reported in the literature for furan[21],thiophen[21] and bromothiophen[22], or of relaxation measurements.

RESULTS AND DISCUSSION

Synthetic aspects

Compounds 2a,2b and 2d were prepared via the corresponding 1,4-diheteroarylbutadiynes 7,6 and 9 respectively,according to a procedure recently employed to synthesize a number of α-thiophen oligomers[13,14] (Scheme 1).

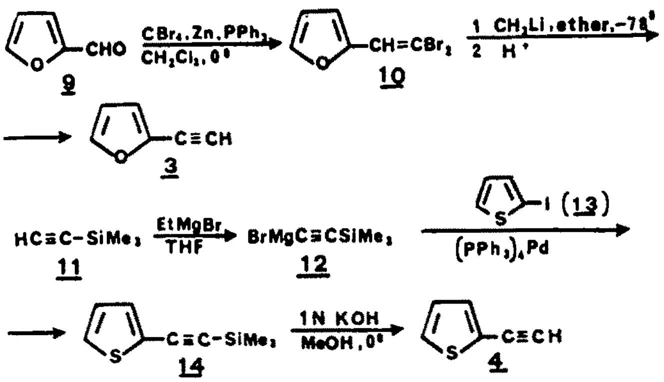
Scheme 1



The symmetrical coupling of 2-ethynylfuran (3) and 2-ethynylthiophen (4) was performed in good yields by the Glaser reaction[23],with CuCl and air.Alternatively,the diynes 5 and 6 were prepared in 90 and 87% yield,respectively,by a novel procedure[24] which consists of reacting benzene solutions of heteroarylacetylenes with one equiv of chloroacetone and two equiv of Et$_3$N,in the presence of a mixture of (PPh$_3$)$_4$Pd and CuI as catalyst.The unsymmetrically substituted diyne 8 was prepared starting from 3 and (2-bromoethynyl)thiophen (7) utilizing the Cadiot-Chodckiewicz procedure[24] (Scheme 1).The cyclization of 5,6 and 8 by treatment with sodium sulfide in refluxing methanol afforded the ter-aryls 2d,2a and 2b in 86, 65 and 87.3% yield, respectively.

The terminal alkyne 4 used to prepare 2b and 2d was synthesized in 81.6% yield starting from furfural (9),according to the method developed by Corey and Fuchs[26],but using methyllithium instead of n-butyllithium(x) (Scheme 2).

Scheme 2



On the other hand,compound 4 was prepared in 83.3% yield by reacting a benzene solution of 2-iodothiophen (13) with a THF solution of trimethylsilylethynylmagnesium bromide (12),in the presence of a catalytic amount of $(PPh_3)_4Pd$,followed by removal of the silyl group from 2-trimethylsilylethynylthiophen (14) so obtained (Scheme 2).

In spite of these good results, we looked for a more general synthetic method that would be suitable to prepare efficiently,in mild experimental conditions,rather unstable π-excessive heteropolyaromatic compounds containing either a functional group,or two or three different heteroarene units. Thus,our attention was directed to the transition metal-catalyzed heteroarylation of heteroaryl halides or dihalides,via cross-coupling reactions with heteroaryl organometallic compounds.It has been in fact reported that Ni- or Pd-phosphine complexes are extremely effective catalysts for the cross-coupling between aryl or heteroaryl organometallic compounds and $C(sp^2)$ halides[27-30].Moreover, these reactions can be efficiently used to prepare mixed heteroarene oligomers containing π-excessive and π-deficient heteroarene components[20].

Therefore,two basic types of cross-coupling reactions were employed:the Ni-phosphine and the Pd-phosphine complex-catalyzed coupling (Scheme 3).

2,2'-Bithienyl (1a) and 2,2':5',2"-terthienyl (2a) were synthesized by reaction of 2-thienyl-magnesium bromide (15) with 2-bromothiophen (16) and 2,5-dibromothiophen (17),respectively, in the presence of a catalytic quantity of $NiCl_2$(dppe) (dppe=$Ph_2P-CH_2-CH_2-PPh_2$) (Scheme 3,eq.a). On the contrary, the preparation of π-excessive heteropolyaromatic compounds containing different heteroarene components was performed by coupling reactions carried out in the presence of a catalytic quantity of $PdCl_2$(dppf) (dppf=1,4-bis(diphenylphosphino)ferrocene).In fact,we had previously observed that the Pd-catalyzed reactions proceed usually in milder conditions than the corresponding Ni-catalyzed reactions and afford comparable or better yields[31].On the other hand,it is known that at least in some cases,$PdCl_2$(dppf) is a catalyst more active and selective than $(PPh_3)_4Pd$, $(PPh_3)_2PdCl_2$ and $PdCl_2$(dppe)[32].

Thus 2-bromofuran (18),2,5-dibromofuran (19) and 2,5-dibromothiophen (17) were coupled in very mild conditions with a molar deficiency of 2-thienylmagnesium bromide (15) to give the cross-coupling

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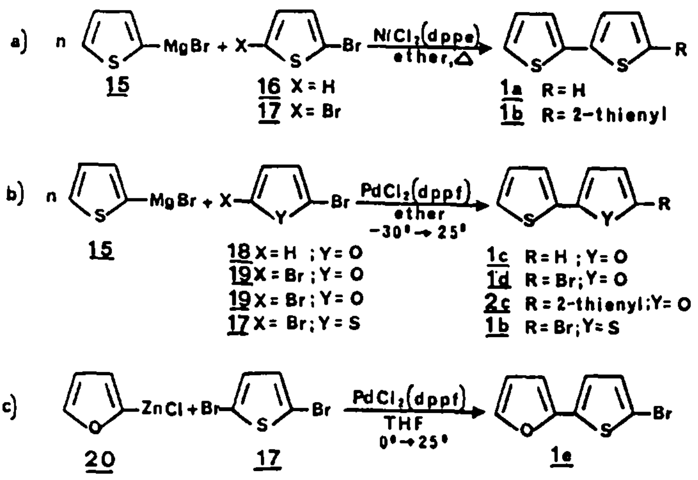
(x) When 2-(2,2-dibromoethenyl)furan (10) was reacted with n-BuLi,the reaction mixture after hydrolysis resulted to contain 1-bromobutane,in addition to the alkyne 3. It was very difficult to obtain pure 3 by fractional distillation of this mixture.

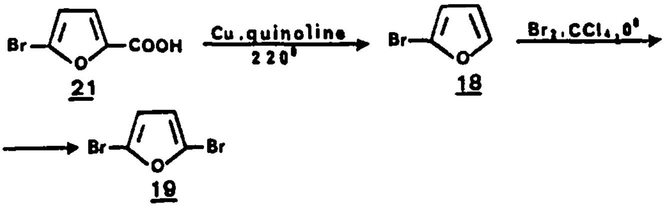
products 1c, 1d and 1b, respectively in satisfactory yields (Scheme 3, eq. b).

Scheme 3



Pure 1d was remarkably unstable even at -25° under nitrogen. However, it was stable in hexane solution even at room temperature. Compounds 19 and 20 were prepared starting from 2-bromo-5-furoic acid (21)[33,34] as shown in Scheme 4.

Scheme 4



Reaction of 19 with a molar excess of 15 gave 2,5-bis-(2-thienyl)furan (2c) in 82% yield (Scheme 3, eq. b).

It is interesting to note that the syntheses of 1b and 1d represent the first examples of rather selective monoheteroarylations of π-excessive heteroaryl dihalides by Grignard reagents. However, such reactions afforded also significant amounts of heteropolyaromatic compounds containing three heteroaryl units, i.e. 2a and 2b, respectively.

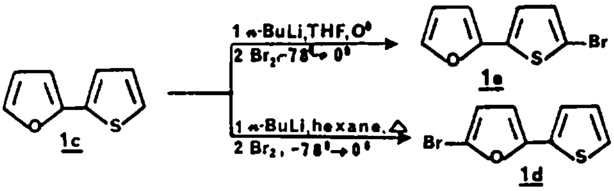
Taking into account these results, the synthesis of 2-bromo-5-(2-furyl)thiophen (1e) was performed using 2-furylzinc chloride (20) as heteroarylating reagent, instead of the corresponding Grignard reagent (Scheme 3, eq. c). It has been reported that in the Pd-catalyzed cross-coupling reactions organozinc compounds lead to higher yields of coupled products with fewer side reactions[15]. Thus, reaction of a THF solution of 2,5-dibromofuran (19) with a molar deficiency of 20, in the presence of $PdCl_2$(dppf), gave compound 1e in 67% yield. However, ca. 20% of the diheteroarylated compound 2c was also isolated in this reaction.

A different approach to 1d and 1e was also attempted. This was based on the selective lithiation of 2-(2-thienyl)furan (1c), followed by bromination. In fact, it is known that in competitive reactions between furan and thiophen for an insufficient quantity of n-BuLi, furan reacts in hexane solution more rapidly than does thiophen[36,37]. On the other hand, thiophen reacts more rapidly than furan under reaction conditions which favour the ionisation of the C-Li bonds[37]. However, in any case the lithiation occurs in the α-position of such heterocycles[36-38]. Thus, taking into account these data, it appeared possible to prepare selectively 1d and 1e starting from 1c.

As expected, reaction of a THF solution of 1c with one equiv of n-BuLi at 0°, followed by bromination gave a reaction mixture which contained ca.11% of unreacted 1c, ca.68.3% of 1e and ca.1.4% of 1d (Scheme 5). Three other unidentified minor components having longer retention times than 1d and 1e on a FFAP capillary column were also present.

On the other hand, with hexane as solvent, the α-lithiation occurred neither at -78°, nor at 0°. However, when the lithiation was carried out for 0.5 hr at the temperature of the refluxing solvent, the reaction mixture, after treatment with bromine, followed by hydrolysis contained 1c and ca.4.5% of 1d (Scheme 5). This result showed that, although the approach based on the selective α-lithiation of 1c was not suitable for preparing 1d, as expected[36,37], the furan ring of 1c reacted in hexane solution more rapidly than the corresponding thiophen ring. Moreover, taking into account the results reported by Chadwick and Willbe[37] for a competitive reaction between furan and thiophen for n-BuLi in experimental conditions similar to those we employed, it appeared that the electrophilic character of 1c towards n-BuLi was rather lower than that one of furan.

Scheme 5



Bioactivity

Bioactivity tests carried out at the Centro Ricerche Antiparassitari of FARMOPLANT (Milan) showed that the heteropolyaromatic compounds 1a and 2a-d and the 1,4-diheteroarylbutadiynes 6 and 9 possessed fungicidal activity. In particular, 2a and 2b exhibited high photo-induced fungitoxicity *in vitro* towards *Pythium irregulare*. On the other hand, compounds 1a, 2b, 2c, 2d, 6 and 9 showed toxicity *in vitro* towards *Botrytis cinerea*, in the absence of long wavelenght ultraviolet light, and 2a displayed phototoxicity in the presence of near UV radiation.

^{13}C NMR measurements

Spectral assignments for most of the ^{13}C signals of 1a-e and 2a-d were made on the basis of previous interpretations of the ^{13}C spectra of furan[21], thiophen[21] and bromothiophen[22]. Ambiguous assignments were verified on the basis of spin-lattice relaxation time (T_1) measurements. In fact, although the T_1 values measured in molecules where internal and anisotropic overall motions are present are not easily interpretable on the basis of the contributions of the various motions[39], ^{13}C T_1 results can be used in a qualitative way to remove ambiguities in the assignments of the individual lines for compounds having an anisotropic overall motion, such as rodlike molecules (e.g. biphenyl)[40]. In these molecules protonated carbons with the C-H direction along the principal inertia axis have in fact a shorter T_1 than those having C-H bonds along the faster rotating perpendicular direction[40,41]. On the other hand, some compounds studied in the present paper were known to present in solution equilibria of planar conformers[42]. In the case of 2,2'-bithienyl (1a) this equilibrium had been studied in detail[42] and the *s-trans*-conformer had been found to be more abundant than the *s-cis* one. For 1a it was therefore likely that carbons in the 5,5'-positions exhibited a shorter relaxation time than those in the 3,3'-positions. In fact, the 3,3' C-H bonds are nearly perpendicular to the principal inertia axis.

A confirmation of this reasoning was found in the case of 2-(2-thienyl)furan (1c).For this molecule no ambiguity arose in the assignment of the ^{13}C signals of the furan moiety (Figure 1). It was therefore significant that the carbon in the 3-position of the furan ring exhibited longer relaxation (6.3) than the carbons in the 4- and 5-positions (4.9 and 5.3,respectively).The C-H bonds in such positions, on account of the conformational equilibrium,are pointed along the principal inertia axis of 1c.On this basis,the signal at 124.09 ppm in 1a was assigned to the carbons in the 5,5'-positions,while the slower relaxing signal at 123.59 ppm was assigned to the carbons in the 3,3'-positions.Assignments of other ambiguous ^{13}C resonances were made analogously and all the results were collected in Figure 1.

A good indication of the consistency of these assignments was that carbons in analogous positions and analogous groups resonated nearly at the same frequency in the various compounds.

On the other hand,the collected T_1 data were also used to obtain qualitative informations on some conformational equilibria.In fact,in the case of 1a for which the *s-trans*-conformer is prevalent,by examinating a molecular model it was possible to see that the C-H bonds in the 5,5'-positions are nearer to the principal inertia axis than the C-H bonds in the 4,4'-positions.Therefore, it was not surprising that the former exhibited a shorter relaxation time.

More evident differences in the relaxation times of carbons in analogous positions to those considered for 1a were observed in compounds containing three heteroaromatic units,such as 2a. By examinating a molecular model of this molecule,in which the first two thiophen rings were placed in a *s-trans* conformation,it was possible in fact to see that the C-H bond in the 5"-position of the third ring is along the principal inertia axis in the *all-s-trans*-conformation. On the contrary, if the third thiophen ring is in a *s-cis*-position with respect to the *s-trans*-bithienyl group,the C-H bond in the 4"-position is placed along the inertia axis.Thus,on the basis of these considerations it was possible to conclude that the *all-s-trans*-conformation prevailed in 2a.

In contrast,in the case of the furyl moieties of 1c,2b and 2d,the carbons in the 4-position had shorter relaxation times than those in the 5-position.This fact could indicate that for these compounds the conformation in which the furan and the thiophen rings are in *s-cis*-position is preferred.

Of course,owing to the complexity of the problem,this is only an hypothesis to be verified by further work.

EXPERIMENTAL

All reactions of air and water sensitive materials were performed in flame-dried glassware under N_2.Glc analyses were performed using a FFAP glass-capillary column (25m x 0.25 mm i.d.).Purifications by liquid chromatography were performed on a Jobin Yvon Chromatospac Prep 10 liquid chromatograph,using a Knauer differential refractometer.

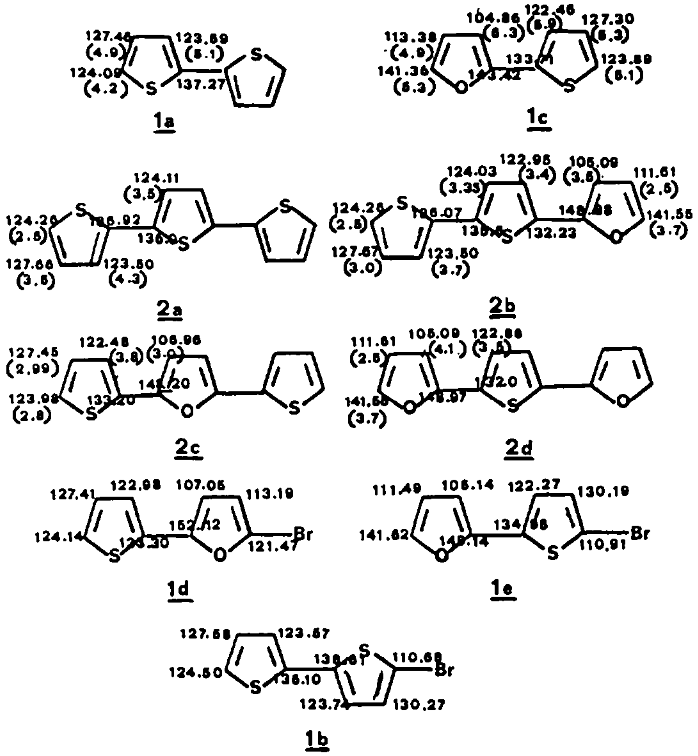
Dichloro[1,2-bis(diphenylphosphino)ethane]nickel (II),dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) and tetrakis(triphenylphosphine)palladium(0) were prepared according to the literature[42.32,44].

^{13}C NMR spectra

The ^{13}C NMR spectra were recorded on a Varian XL-100 spectrometer operating at 25.16 MHz,by a proton noise decoupled ^{13}C Fourier transform operation,using a computer-controlled system.The spectra were registered for $CDCl_3$ solns containing TMS as an internal standard,unless otherwise indicated. The spin-lattice relaxation times (T_1) for all the protonated carbons were determined simultaneously by the standard inversion recovery pulse method.The standard Freeman-Hill program was used to analyze the data. The samples were carefully degassed prior to the experiments. A reproducibility of the T_1 values better than ± 10% was obtained in most cases. The chemical shift data for all carbons and the T_1 data for protonated carbons are reported in Figure 1.A sample of 2b was also studied at 100 MHz on a Varian XL-400 spectrometer. The obtained T_1 values paralleled satisfactory those obtained at 25.16 MHz.

Figure 1

Assignment of the ^{13}C NMR chemical shifts of 1a-e and 2a-d. The spin-lattice relaxation times (T_1) are reported in parenthesis.$^{x)}$



x)The spectra of 1a,1b,1c,1e and 2a-d were registered for $CDCl_3$ solns. The spectrum of 1d was registered for an hexane soln.

2-Ethynylthiophen (4)

Trimethylsilylacetylene (10.63 g,0.108 mol) was added to a soln of ethylmagnesium bromide (0.120 mol) in THF (180 ml).After the addition was complete, heating was continued for 1 hr.The THF soln of the so obtained trimethylsilylethynylmagnesium bromide was then slowly added to a mixture of 2-iodothiophen (13)(21 g,0.1 mol) and $(PPh_3)_4Pd$ (2.52 g, 2.23 mmol) in benzene (150 ml).After the addition was complete,the mixture was stirred for 16 hr at room temp and for 1 hr at 60°. It was then cooled to room temp and hydrolyzed with sat NH_4Cl aq.After usual work up,the reaction mixture was fractionally distilled to afford 2-trimethylsilylethynylthiophen (14)(17.8 g, 98% yield):b.p. 104°/15 torr; ^1H NMR (CCl_4): δ 0.20 (s,9H),6.83-7.13 ppm (m,3H).Compound 14 (16.01 g, 0.088 mol) was then dissolved into methanol (80 ml) and treated at 0° under N_2 with 1N KOH aq (88 ml).The mixture was stirred for 2 hr at room temp and extracted with pentane.The organic layer was washed with sat NaCl aq,filtered,dried and concentrated.The residue was fractionally distilled to afford 4 (8.19 g, 85% yield):b.p. 53-54°/25 torr; ^1H NMR (CCl_4): δ 3.25 (s,1H), 6.83-7.35 ppm (m, 3H).[Lit^{14} b.p. 46°/15 torr].

2-(2,2-Dibromoethenyl)furan (10)

Triphenylphosphine (65.40 g, 0.219 mol),carbon tetrabromide (82.27 g, 0.248 mol) and zinc dust (19.2 g, 0.299 mol) were placed in a well dried 1l round-bottomed flask.Anydrous dichloromethane (600 ml) was then added under N_2 and the mixture was stirred for 38 hr at room temp. Furfural (9) (9.57 g, 99.6 mmol) was then slowly added to the stirred mixture cooled at 0°. After stirring for 6 hr at room temp,the reaction mixture was extracted with hexane according to the original report^{26}. The hexane extract was concentrated *in vacuo* to afford a residue (21.2 g, 85% yield) which was used in the next step without any further purification. Glc analysis showed that this residue did not contain unreacted 9 and was constituted by a single compound having ca. 95% chemical purity. Part of this residue (1 g) was however purified by chromatography on a Merck H 60 silica gel column,using hexane as eluant. Pure 10 had: ^1H NMR (CCl_4): δ 7.33 (m,2H), 6.91 (br d, 1H),6.40 ppm (m, 1H). IR(neat): ν_{max} 3150,3120,3040,2960,2860,2660,2560,2460,1740,1675,1610,1560,1545,1480,1380, 1285,1260,1235,1210,1170,1150,1140,1085,1020,945,928,882,845,830,805,740,695,and 590 cm^{-1}. (Found: C,28.51;H,1.53;Br,63.25. Calc for $C_6H_3Br_2O$:C,28.61; H,1.60; Br, 63.44).

2-Ethynylfuran (3)

A soln of crude 10 (25.89 g, 0.103 mol) in 1l of dry ether was cooled to -78° under N_2 and a 2.3M ether soln of methyllithium (125.2 ml, 0.288 mol) was added dropwise.After stirring for 1 hr at -78°,the mixture was allowed to warm up to room temp and was stirred for 1 hr longer.The mixture was treated as usual[26] and finally distilled to produce 3 (9.19 g, 96% yield):b.p. 81-82°/262 torr. ^{1}H NMR (CCl_4): δ 3.25 (s,1H),6.46(dd,1H),6.55(d,1H),7.28 ppm (m,1H). [Lit[47] b.p. 55°/124 torr].

1,4-Bis-(2-thienyl)butadiyne (6)

(Method A) Compound 6 was prepared in 87% yield by the Glaser reaction starting from 4,according to the procedure described in the literature[14].Compound 6 had:m.p. 92.5-93°. [Lit[14] m.p.92-93°].

(Method B) Triethylamine (10.12 g,0.1 mol) was added under N_2 to a stirred mixture of $(PPh_3)_4Pd$ (1.17 g, 1.01 mmol) and CuI (0.72 g,3.79 mmol) in dry benzene (20 mo). This mixture was sequentially treated with chloroacetone (4.63 g,0.050 mol) and 2-ethynylthiophen (4)(5.4 g,0.050 mol). After stirring for 16 hr at room temp, a NH_4Cl sat aqueous soln was added and the mixture was extracted with benzene.The filtered extract was concentrated and the residue was purified by chromatography on a silica gel column using hexane as eluant to afford 6 in 87% yield:m.p. 92.5-93°.

1,4-Bis-(2-furyl)butadiyne (5)

(Method A) Compound 5 was prepared in 88% yield by the Glaser reaction starting from 3 and following a procedure identical to that employed to prepare 6. Compound 5 had: m.p. 49-51°; ^{1}H NMR (CCl_4): δ 7.33(d,2H),6.70(d,2H),6.53-6.30 ppm (m, 2H). IR(KBr): ν_{max} 3140,3120,1740,1640,1570,1500, 1470,1375,1200,1140,1070,1015,925,890,820,740,585 cm^{-1}. (Found:C,78.74; H,3.37; Calc for $C_{12}H_6O_2$: C,79.12; H,3.32).

(Method B) Compound 5 was prepared in 90% yield by reaction of a benzene soln of 3 with one equiv of chloroacetone and two equiv of Et_3N, using a mixture of $(PPh_3)_4Pd$ and CuI as catalyst.The procedure was identical to that employed to prepare 6.Compound 5 had: m.p. 49-51°.

1-(2-Thienyl)-4-(2-furyl)butadiyne (8)

Bromine (12.1 g, 75.6 mmol) was added to a mixture of ice-water (35 g) and 10N NaOH aq (17.4 ml, 0.174 mol).2-Ethynylthiophen (4)(7.5 g,69.4 mmol) in THF (5 ml) was dropwise added to the mixture maintaining at 0°. After stirring for 6 hr at room temp the mixture was poured into a sat NH_4Cl aq soln and extracted with ether.The extract was washed until neutrality and dried over Na_2SO_4. The solvent was removed at 300 torr at room temp to afford a residue (ca.13 g) which was constituted essentially of (2-bromoethynyl)thiophen (7).

Butylamine (25.68 g,0.351 mol) was added under N_2 at 0° to a mixture of CuCl (142.8 mg, 1.44 mmol) and $NH_2OH \cdot HCl$ (8.38 g,0.120 mol).This mixture was stirred for 10 min at 0° and then slowly added to a soln of 2-ethynylfuran (3)(6.38 g,0.069 mol) in EtOH (140 ml) maintained at 15°. A soln of 7 (13.0 g,69.4 mmol) in EtOH (70 ml) was then added during 4 hr to the stirred mixture.After stirring for 1 hr longer,the reaction mixture was poured into water and extracted with hexane.The extracts were washed with sat NH_4Cl soln,dried over Na_2SO_4 containing K_2CO_3,and concentrated to afford a solid residue (10.37 g)(m.p.45-55°) which was purified by chromatography on a silica gel column using hexane as eluant.Compound 8 (8.01 g, 58% yield) had: m.p. 53.5-55°; IR(KBr): ν_{max} 3140,3100, 2910,2840,2200,2140,1475,1420,1360,1300,1290,1225,1210,1175,1145,1070,1945,1015,950,890,850,840, 820,750,710,and 590 cm^{-1}. ^{1}H NMR (CCl_4): δ 7.5-7.3 (m,3H),7.1-6.8 (m,1H), 6.67(d,1H),6.35 ppm (dd, 1H). ^{13}C NMR ($CDCl_3$): δ 144.52,136.24,134.47,128.96,127.03,118.19,111.06, 157.54 ppm. (Found: C, 72.46; H,2.88; S,15.90. Calc . for $C_{12}H_6OS$:C,72.71; H,3.05; S,16.17). Glc analysis showed that 8 was chemically pure.

2-Bromofuran (18)

According to the literature[34],5-bromo-2-furoic acid (21) (5 g,26.2 mmol),quinoline (10 g,77 mmol) and copper powder (1 g) were reacted at 210° in a round bottomed flask bearing a short Vigreux column which was connected to a small condenser and a receiver for the liquid distillate.2-Bromofuran (18) distilled into the receiving flask.When 21 was completely decarboxylated,as shown by cessation of gas evolution,the flask was allowed to cool.A second portion of 21 (5 g,26.2 mmol)was added and the process repeated.In this way 25 g of the acid could be decarboxylated before dismantling the apparatus.The distillate was dried overnight on CaH_2 and then distilled to afford 18 in 75% yield:b.p.100-101°; ^{1}H NMR(CCl_4): δ 6.23 (m,2H),7.33 ppm(dd,1H). [Lit[34] b.p.101.9-102.2°].Glc analysis showed thet 18 had chemical purity higher than 99%.

2,5-Dibromofuran (19)

According to the literature[35],a soln of bromine (8.4 g,52.5 mmol) in CCl_4(27 ml) was dropwise added to a stirred soln of 18 (7.49 g,50.5 mmol) in CCl_4(27 ml) which was maintained at 0°.The reaction mixture was then poured into a 10% Na_2CO_3 aq soln cooled at 0° and extracted with CCl_4.The organic extracts were dried, concentrated and distilled to afford 19 (8.00 g, 71% yield): b.p. 53°/15 torr. [Lit[35] b.p. 64°/20 torr]. Glc analysis showed that 19 had chemical purity higher than 97%.

Cyclization of the 1,4-diheteroarylbutadiynes 5,6 and 8 into the 2,5-disubstituted thiophens 2d, 2a and 2b, respectively.

A mixture of 6 (7.70 g, 0.036 mol), $Na_2S\cdot9H_2O$ (34.32 g, 0.143 mol) and methanol (600 ml) was refluxed overnight under N_2. The soln was cooled and concentrated *in vacuo* at room temp. The residue was diluted with hexane, washed with water, dried and concentrated. The solid so obtained was recrystallized from 95% EtOH to give 2,2':5',2"-terthiophen (2a) (7.67 g, 86% yield): m.p. 93-94°. ^{13}C NMR ($CDCl_3$): 136.97, 136.01, 127.66, 124.26, 124.11, 123.50 ppm. Lit[14] m.p. 93-94°.

2,5-Bis(2-furyl)thiophen (2d) was prepared in 65% yield fro 5, using the above described procedure: m.p. 67-69°; IR(KBr): ν_{max} 3100, 1770, 1730, 1715, 1580, 1520, 1490, 1475, 1455, 1430, 1330, 1200, 1150, 1140, 1060, 1010, 980, 968, 882, 805, 795, 722, 660, 585 cm^{-1}. ^{1}H NMR (CCl_4): δ 7.33 (d, 2H), 7.08 (d, 2H), 6.37 ppm (br s, 4H). ^{13}C NMR ($CDCl_3$): δ 148.97, 141.55, 132.09, 122.86, 111.61, 105.09 ppm. (Found: C, 66.69; H, 3.61. S, 14.68. Calc. for $C_{12}H_8O_2S$: C, 66.66; H, 3.73; S, 14.83). Glc analysis showed that 2d was chemically pure.

Crude 2-(2-thienyl)-5-(2-furyl)thiophen (2b) was prepared starting from 8 using the above described procedure. Compound 2b was purified by chromatography on a silica gel column using hexane as eluant. The yield was 87.3%. Pure 2b had: m.p. 83-85°; ^{1}H NMR (CCl_4): δ 7.33 (br, 1H), 7.30-6.8 (m, 5H), 6.40 ppm (br s 2H). ^{13}C NMR ($CDCl_3$): δ 148.88, 141.55, 136.07, 135.89, 132.23, 126.67, 124.26, 124.03, 123.50, 122.95, 111.61, 111.44, 105.09 ppm. (Found: C, 62.18; H, 3.58. Calc. for $C_{12}H_8OS_2$: C, 62.04; H, 3.47). Glc analysis showed that 2b was chemically pure.

Coupling reaction of heteroarene halides with heteroaryl Grignard reagents in the presence of $NiCl_2$(dppe): 2,2'-dithienyl (1a) and 2,2':5',2"-terthiophen (2a).

In a typical experiment a soln of 2-thienylmagnesium bromide (15) (0.22 mol) in ether was dropwise added to a mixture of 2-bromothiophen (16) (32.6 g, 0.20 mol) and $NiCl_2$(dppe) (0.60 g) in dry ether (150 ml). The mixture was refluxed for 5 hr, hydrolyzed with sat NH_4Cl aq and then extracted with ether. Fractional distillation of the dried extract gave 1a in 90% yield: b.p. 125°/12 torr; m.p. 33°; ^{13}C NMR ($CDCl_3$): δ 137.27, 127.46, 124.09, 123.59 ppm. [Lit[46] m.p. 33°].

According to this procedure 2,2':5',2"-terthiophen (2a) was prepared in 70% yield by reacting an ether soln of 15 (62 mmol) with a THF soln of 2,5-dibromothiophen (17) (25 mmol) in the presence of $NiCl_2$(dppe) (0.3 mmol). Compound 2a (m.p. 93-94°) had spectral properties identical to those of 2a prepared starting from the diyne 6.

2-(2-Thienyl)furan (1c)

A soln of 15 (0.111 mol) in ether (140 ml) was dropwise added to a stirred soln of 2-bromofuran (18) (12.3 g, 85 mmol) and $PdCl_2$(dppf) (622 mg, 0.86 mmol) in dry ether (70 ml) cooled to -30°. The reaction mixture was then stirred at room temp for 5 hr, hydrolyzed with sat NH_4Cl aq and then extracted with ether. The extracts were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. Fractional distillation of the residue afforded 1c (12.53 g, 98% yield): b.p. 103°/15 torr; ^{1}H NMR (CCl_4): δ 7.28 (m, 1H), 7.25-6.75 (m, 3H), 6.33 ppm (m, 2H). IR(neat): ν_{max} 3150, 3110, 3080, 1795, 1735, 1650, 1610, 1590, 1525, 1490, 1480, 1425, 1380, 1350, 1260, 1235, 1205, 1150, 1080, 1070, 1045, 1015, 990, 980, 880, 845, 825, 795, 730, 690, 660, 640, 590 cm^{-1}. ^{13}C NMR ($CDCl_3$); δ 149.42, 141.36, 133.71, 127.30, 123.89, 122.46, 111.38, 104.86 ppm. [Lit[16] b.p. 118-120°/10 torr]. Glc analysis showed that compound 1c was chemically pure.

2,5-Bis-(2-thienyl)furan (2c)

A soln of 15 (57.3 mmol) in ether (70 ml) was added during 0.5 hr to a stirred mixture of 2,5-dibromofuran (19) (4.8 g, 21.2 mmol) and $PdCl_2$(dppf) (298 mg, 0.41 mmol) in dry ether (36 ml) cooled to -30°. After the mixture was stirred for 2.5 hr at room temp, the reaction work up was as above. The dried organic phase was concentrated *in vacuo* and purified by liquid chromatography using hexane as eluant, to give 2c (4.03 g, 82% yield): m.p. 81-83°; ^{1}H NMR (CCl_4): δ 7.35-6.8 (m, 6H), 6.43 ppm ((m, 2H). ^{13}C NMR ($CDCl_3$): δ 148.29, 133.20, 127.45, 123.98, 122.48, 106.96 ppm. (Found: C, 62.38; H, 3.44. Calc. for $C_{12}H_8OS_2$: C, 62.04; H, 3.47). Glc analysis showed that 2c had chemical purity higher than 98%.

2-Bromo-5-(2-thienyl)furan (1d)

According to the above described procedure, a soln of 15 (80 mmol) in ether (120 ml) was reacted with a mixture of 2,5-dibromofuran (19) (16.7 g, 73.9 mmol) and $PdCl_2$(dppf) (540 mg, 0.0739 mmol) in ether (100 ml) cooled to -30°. After the mixture was stirred for 2.5 hr at -10° and 1 hr at room temp the reaction work up was as above. After partial elimination of the solvent at room temp, the residue was purified by liquid chromatography on a silica gel column, using hexane as eluant. Compound 1d was the most mobile component of the crude reaction mixture. Owing to its instability, its yield was evaluated by glc analysis of the hexane soln obtained from the chromatography. The spectral properties of 1d were also determined in hexane soln. In fact, homogeneous 1d decomposed quickly even at -20° under N_2 and in the presence of K_2CO_3. ^{13}C NMR (hexane): δ 152.12, 133.30, 127.41, 124.14, 122.98,121.47,113.19,107.05 ppm.MS (m/e):232(0.3),231(0.6),230(6.2),149(6.5),123(4.8),122(9.2),121 (100),93(5.1),82(4.6),77(14.7),69(11.7),63(11.9),50(12.3),45(27.3).IR(hexane): ν_{max} 1540,1425,1305, 1255,1190,925,840,770,690 cm^{-1}.

The last collected fractions of the chromatography contained compound 2c (2.47 g).The spectral properties of 2c were identical to those above reported.

2-Bromo-5-(2-thienyl)thiophen (1b)

This compound was prepared according to the same procedure used for the synthesis of 1d,starting from 15 (98 mmol) and 2,5-dibromothiophen (17) (29.4 g,0.13 mol).The crude reaction mixture was purified by chromatography on a silica gel column,using hexane as eluant,to give 1b (13.8 g,58% yield):m.p.32-33°; ^{13}C NMR($CDCl_3$): δ 110.68,123.57,123.74,124.50,127.58,130.27,136.10,138.61 ppm. [Lit[19] m.p.30-33°].

Liquid chromatography allowed also to recover compound 2a (4.15 g,34.2% yield) which had spectral properties identical to those above reported.

2-Bromo-5-(2-furyl)thiophen (1e)

A I.6M soln of n-BuLi in hexane (45.8 ml,73.3 mmol) was dropwise added to an ice-cooled soln of furan (5.44 g,80 mmol) in dry THF (80 ml).After the addition ,the soln was allowed to stir at 0° for 3.5 hr and then added to an ice-cooled soln of $ZnCl_2$ (10.5 g,75 mmol) in THF (60 ml).The resulting mixture was stirred for 0.5 hr at 0° and then added during 3.5 hr to a mixture of 2,5-dibromothiophen (19)(21.78 g,90 mmol)and $PdCl_2$(dppf)(585 mg,0.8 mmol) in THF (100 ml).After the mixture was stirred for 0.5 hr at 0° and 15 hr at room temp,the reaction work up was as above.Glc analysis of the crude reaction mixture showed the presence of unreacted 19,of 2,5-bis-(2-furyl)-thiophen (2c),and of a new compound,(1e).Purification by chromatography on a silica gel column using hexane as eluant allowed to recover 1e (11.25 g,67% yield):IR(neat): ν_{max} 3150,3130,3090, 1725,1650,1600,1590,1525,1490,1460,1425,1375,1325,1250,1220,1200,1070,1055,1010,985,955,880,870, 785,725,655,685 cm^{-1}. ^1H NMR(CCl_4): δ 7.34-7.23(m,1H),6.86(s,2H),6.40-6.24 ppm(m,2H). ^{13}C NMR($CDCl_3$): δ 148.14,141.62,134.98,130.19,122.27,111.49,110.91,105.14 ppm.MS(m/e):232(2.5),231(5.1),230(44.6), 228,(44.6),202(1.1),201(10.3),199(9.7),150(0.9),149(8.0),125(1.2),123(6.5),122(10.6),121(100),119 (6.9),117(3.7),115(4.1),114(4.0),105(3.7),95(5.4),94(4.9),93(8.0),92(2.8),82(7.1),81(4.9),77(18.8), 74(6.0),69(13.6),63(12.2),51(11.0),45(16.3).(Found:C,42.01; H,2.22.Calc. for C_8H_5BrOS:C,41.94;H, 2.20).Glc analysis showed that compound 1e was chemically pure.

Liquid chromatography also allowed to recover chemically pure 2c (1.6 g).

2-Bromo-5-(2-furyl)thiophen (1e) by metallation of 1c followed by bromination.

A 1.6M soln of n-BuLi (2.38 ml),3.8 mmol) was added under N_2 to a soln of 2-(2-thienyl)furan (1c) (570 mg,3.8 mmol) in THF (15 ml) cooled to 0°.The mixture was stirred for 4 hr at 0°,then cooled to -78°.Bromine (608 mg,3.8 mmol) was added and the resulting mixture was stirred for 10 min at 0°. It was then poured into ice-water and extracted with ether.The extracts were washed with water and dried over Na_2SO_4 containing K_2CO_3.Glc analysis showed that the reaction mixture contained ca.11% of 1c,ca.68.3% of 1e,ca.1.4% of 1d,and three other unidentified minor components having longer retention times than 1d and 1e.

2-Bromo-5-(2-thienyl)furan (1d) by metallation of 1c followed by bromination.

A 1.6M hexane soln of n-BuLi (2.71 ml,4.33 mmol) was added under N_2 to a soln of 1c (650 mg,4.33 mmol) in hexane (13 ml).The mixture was refluxed for 0.5 hr under stirring,then cooled to -78°. Bromine (693 mg,4.33 mmol) was added and the resulting mixture was stirred for 10 min at 0°.It was then poured into ice-water and extracted with ether.The extracts were washed with water and dried over Na_2SO_4 containing K_2CO_3.Glc analysis showed that the reaction mixture contained ca.95.5% of 1c and 4.5% of 1d.

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