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Highly Efficient Non-Palladium-Catalyzed Controlled Synthesis and X-ray Analysis of Functionalized 1,2-Diaryl-, 1,2,3-Triaryl-, and 1,2,3,4-Tetraarylbenzenes**

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Abstract: A general, two-step, highly efficient synthesis of 1,2-diaryl-, 1,2,3-triaryl-, and 1,2,3,4-tetraarylbenzenes from simple stitching of α-oxo-ketene-*S,S*-acetals and active methylene compounds via a lactone intermediate is described. This procedure offers easy access to highly functionalized arylated benzenes that contain sterically demanding groups in good to excellent yields. The novelty of the procedure lies in the construction of aromatic compounds with the desired conformational flexibility along the molecular axis in a transition-metal-free environment through easily accessible precursors. Crystal analysis of these arylated benzene scaffolds showed that the peripheral aryl rings are arranged in a propeller-like fashion with respect to the central benzene ring. Examination of the crystal packing in the structure of a 1,2,3,4-tetraarylbenzene revealed an N···π interaction between molecules related by a two-fold screw axis running in the direction of the *a* axis. Interestingly, the repeating array of N···π interactions around the axis of this 1,2,3,4-tetraarylbenzene forces the molecules into a helical pattern.

Keywords: arylbenzenes · lactones · N–pi interactions · ring transformation · X-ray diffraction

Introduction

The demand for functionally congested biaryl compounds for both synthetic and medicinal purposes has increased dramatically during the past few decades. Besides their great diversity in complex natural products[1] and pharmaceutical agents,[2] these compounds are fascinating and challenging research objects in materials[3] and polymer sciences.[4] Axially chiral biaryls are useful as versatile auxiliaries for asymmetric synthesis,[5] as chiral phases for chromatography,[6] and as important substrates for chiral liquid-crystalline materials.[7] Recently, numerous natural products with terphenyl architecture have been reported with interesting biological properties.[8–11] Several synthetic terphenyl derivatives have been designed as selective inhibitors for dihydroortate dehydrogenase[12] and cyclooxygenase[13] enzymes. Terphenyls that contain acidic groups were recently found to be potent insulin sensitizers.[14] Owing to their interesting optical[15] and electrical[16] properties, terphenyls find several industrial applications as liquid crystals, conducting polymers, heat storage and transfer agents, textile dye carriers, and laser dyes. Recently a great deal of attention has been focused on the construction of useful teraryl- or tetraarylbenzene building blocks with electron-withdrawing and -releasing groups for preparing advanced electroluminescent materials.[17]

Limited procedures are known for the synthesis of such biaryls in which one of the aryl rings is functionalized with two or more aromatic rings in a juxtaposed manner. Palladium-catalyzed aryl–aryl cross-coupling between the electrophilic aromatic halides ArX_n (X being generally Br, I, and OTf; *n* being mainly 0, 1, or 2) and organometallic species ArM (M being Mg, Ni, Zn, Sn, and B) is a versatile synthetic method for the preparation of diverse arylated benzenes.[18] Of the various coupling reactions, the Pd-catalyzed Suzuki–Miyaura couplings of a wide array of haloarenes with arylboronic acids has dominated this area owing to the commercial availability and innocuous nature of the latter, easy workup, and tolerance of the reactions to aqueous

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media. Diarylbenzenes have been synthesized either by the coupling of biaryltriflate compounds with Grignard reagents in the presence of a palladium catalyst in moderate to good yields,[19] or by the iterative coupling of arylboronic acid with aromatic halides[20] separately. Despite the wide synthetic generality of these aryl–aryl cross-coupling reactions, multiple coupling on tri- or tetrahalides to prepare triaryl- or tetraarylbenzenes places constraints on the choice of reagents or catalysts and either produces low yields of desired compounds or fails completely to fulfill the demand.

Although numerous nonmetal-catalyzed approaches, particularly regio- and stereoselective Diels–Alder cycloadditions[21] of 2*H*-pyran-2-ones with electron-deficient and electron-rich dienophiles, do exist in the literature, they require forcing thermal conditions and/or do not provide a general route for preparing di-, tri-, or polyarylbenzenes. The wide-ranging applications and high demand of arylated benzenes and paucity of nonmetal-catalyzed synthetic methodologies prompted us to develop a simple, general, and efficient route that could offer the flexibility of substituent variation on the benzene scaffold. Herein, we report a highly convenient and commercially viable synthetic route for 1,2-diaryl-, 1,2,3- and 1,2,4-triaryl-, and 1,2,3,4-tetraarylbenzenes through simple stitching of α-oxo-ketene-*S,S*-acetals with active methylene molecular pieces (malononitrile, 2-methoxyacetophenone, or deoxybenzoin) in just two steps. The versatility and generality of the procedure lies in the creation of a central benzene ring with optional di-, tri-, and tetraaryl moieties in a controlled fashion in an organometallic-reagent-free environment.

Results and Discussion

Chemistry

During the recent studies on the chemistry of 2*H*-pyran-2-ones, we observed[22] that 2*H*-pyran-2-ones prepared from α-oxo-ketene-*S,S*-acetal[23] **1** have promising structural topology as useful substrates for ring transformation reactions, a flexible substitution pattern, and the presence of a good leaving alkylsulfanyl group for generating molecular diversity. Our initial efforts indicated[24] that the α-pyranone ring can be converted into a benzene ring under mild basic conditions. Such a new ring transformation[25] (recently termed lactone methodology) prompted us to explore the route for preparing bent-cored oligopyridine[26] and oligophenylene[27] as useful building blocks for advanced materials. Recently, we exploited our lactone methodology to synthesize biaryls with acetyltrimethylsilane as a carbanion source.[28]

Our previous efforts were on preparing simple aromatic systems, and now we have systematically prepared functionally congested 1,2-diaryl-, 1,2,3-triaryl-, and 1,2,3,4-tetraarylbenzenes, which are difficult to prepare by conventional routes, in just two steps. All these compounds are novel and have not been reported prior to this study.

Our aim of synthesizing functional-group-containing 1,2-diarylbenzenes was achieved by preparing the key intermediate α-cyano-ketene-*S,S*-acetal **1** from easily accessible precursors methyl cyanoacetate, carbon disulfide, and methyl iodide through a modified procedure.[29] The α-cyano-ketene-*S,S*-acetal **1**, upon Michael addition and cyclization with various substituted deoxybenzoins **2a–f** under alkaline conditions, furnished 5,6-diaryl-2*H*-pyran-2-ones **3a–f** in excellent yields (Table 1). Various functionalized deoxybenzoins were prepared by heating a mixture of functionalized phenyl acetic acid and substituted benzenes in polyphosphoric acid as described previously.[30] The 5,6-diaryllactones **3a–f** generated from **1** have promising structural topology as useful substrates for Michael addition reactions, dense and flexible substitution patterns, and the presence of a good leaving alkylsulfanyl group for generating molecular or functional-group diversity.

Our approach to preparing 1,2-diarylbenzenes involved stirring an equimolar mixture of 2*H*-pyran-2-ones **3a–f**, malononitrile, and powdered KOH in DMF for 12–15 h at room temperature to afford functionalized 1,2-diarylbenzenes **4a–f** in 89–94% yields (Table 1). Notably, functional groups such as methylsulfanyl, cyano, and amine groups can be removed (desulfurization, decyanation, deamination) or modified depending upon the desired diarylbenzene compounds.[31]

A plausible reaction mechanism for the formation of functionalized 1,2-diarylbenzenes **4a–f** is based on Michael–Ziegler–Thorpe retro-Diels–Alder type reaction of **1** with an active methylene compound under mild reaction conditions as depicted in Table 1. The reaction is initiated by the Michael addition of an anion, generated from a molecule of deoxybenzoin **2**, to the ketene-*S,S*-acetal **1** followed by intramolecular cyclization to form a 2*H*-pyran-2-one intermediate **3**. The lactone **3** has three electrophilic centers, C2, C4, and C6, of which C6 is likely to be highly electrophilic due to extended conjugation and the presence of an electron-withdrawing nitrile group at position 3. The 2*H*-pyran-2-one is attacked by a malononitrile anion at C6, followed

Abstract in Hindi:

एल्फा-आक्सो-कीटीन-S-S-एसीटल और क्रियाशील मिथाइलीन यौगिकों की एक माध्यमी लैक्टोन से सामान्य विधि द्वारा 1,2-द्विएरिल, 1,2,3-त्रिएरिल और 1,2,3,4-चतुर्थएरिलबेन्जीन का एक सामान्य द्वि-पदीय अति विशिष्ट संश्लेषण वर्णित है। यह विधि अति बाधित-इष्टिस्त समूह युक्त एरीलेटेड-बेन्जीन को अत्यधिक मात्रा में निर्माण हेतु सहायक है। एक संक्रमण धातु-मुक्त वातावरण में सरलता से प्राप्त यौगिक के द्वारा यौगिकीय अक्ष पर इष्टिस्त सनरूपण नम्यता के साथ ऐरोमेटिक यौगिकों का निर्माण, इस विधि की नवीनता है। ऐरीलेटेड बेन्जीन यौगिकों का स्फटिक अध्ययन, परिधीय ऐरिल वक्रों का प्रोपेलर की आकृति में, मध्य बेन्जीन वक्रों के परिप्रेक्ष्य में व्यवस्थिति प्रदर्शित करता है। एक यौगिक 12 सी के स्फटिक अनुबन्धन के अध्ययन से यह स्पष्ट होता है कि यौगिकों में पेंचनुमा द्वि-पटल अक्षीय N...π अन्योन्य प्रभाव उपस्थित है। यह N...π पुनरावृत्ति, 1,2,3,4-चतुर्थएरिल बेन्जीन 12 सी के अक्ष के चारों ओर वक्राकार आकृति के लिए बाध्य करती है।

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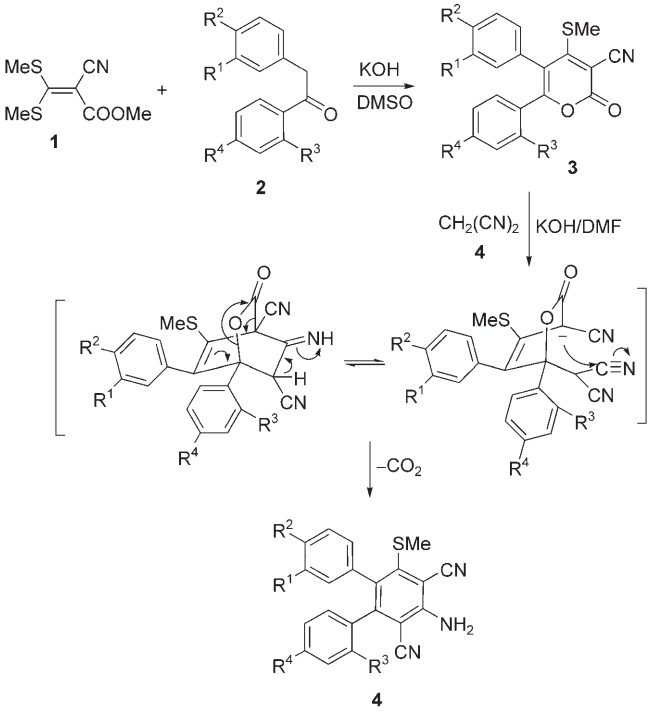
Table 1. Synthesis of 1,2-diarylbenzenes.[a]



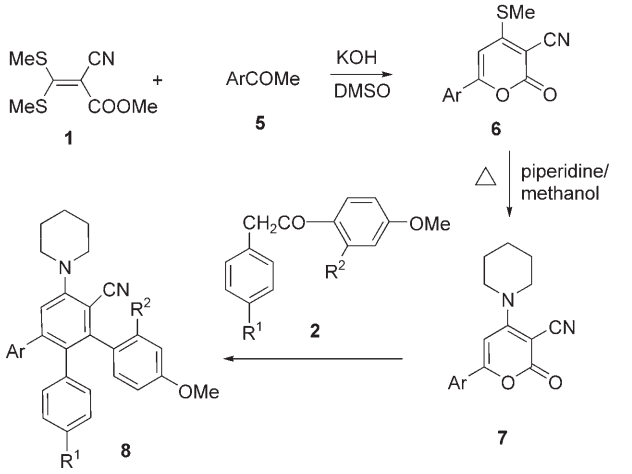
Compound	R^1	R^2	R^3	R^4	Yield [%]	
					3	**4**
a	H	H	H	H	91	90
b	H	H	H	OMe	88	91
c	H	F	OMe	OMe	83	94
d	H	OMe	H	OMe	90	89
e	OMe	OMe	H	OMe	87	92
f	H	F	H	OMe	86	90

[a] DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide.

first by Thorpe cyclization involving one of the nitrile functionalities of malononitrile and C3 of the pyranone ring to form a bicyclic intermediate and then by decarboxylation to furnish 1,2-diarylbenzene **3** in high yield.

To exploit the methodology for preparing useful 1,2,3-triarylbenzene compounds, ketene dithioacetal **1** was treated with functionalized acetophenones **5a–d**, which furnished 6-aryl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitriles **6a–d** in high yields (Table 2). To prepare compounds with amine functionality, the good leaving methylsulfanyl group of lactones **6a–d** was replaced with various secondary amines. We prepared 6-aryl-2-oxo-4-piperidin-1-yl-2*H*-pyran-3-carbonitriles **7a–d** in good yields by heating a mixture of **6a–d** at reflux with piperidine in methanol. Compounds **7a–d** reacted with functionalized deoxybenzoins **2** to yield 4-cyano-5-(piperidin-1-yl)-1,2,3-triarylbenzenes **8a–d** in excellent yields. All the compounds were characterized by spectroscopic analysis. Notably, the reaction proceeded smoothly even with the bulky naphthalene moiety, which furnished 1,2,3-triarylbenzene **8d** in 91% yield. This approach provides the flexibility of introducing a secondary amine group into the central benzene ring of 1,2,3-triarylbenzene. Furthermore, the reaction can tolerate unprotected hydroxy

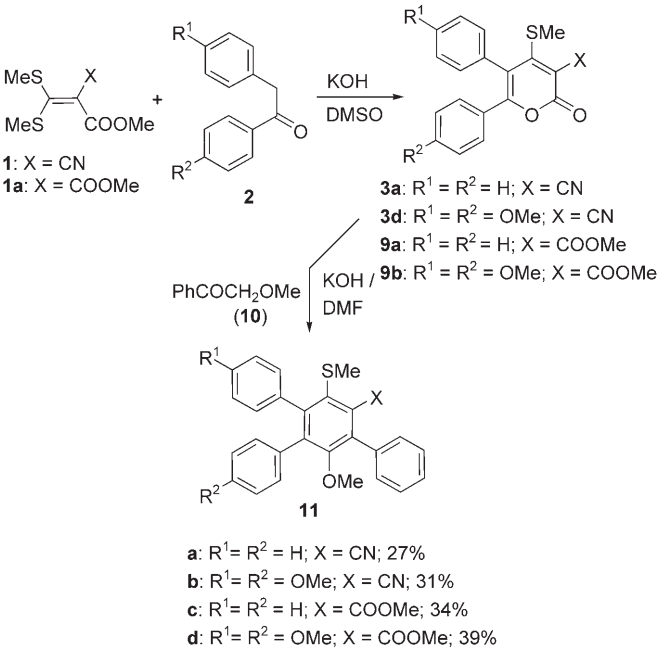
Table 2. Synthesis of 1,2,3-triarylbenzenes.



8	Ar	R^1	R^2	Yield [%]
a	4-MeC_6H_4	H	OH	94
b	thienyl	H	OH	87
c	4-FC_6H_4	OMe	H	90
d	1-naphthyl	OMe	H	91

groups (R^2 = OH), particularly at the sterically hindered *ortho*-position.

To explore this reaction further for the preparation of 1,2,4-triarylbenzenes, we carried out the reaction of 5,6-diaryl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitriles **3a** and **3d** or 5,6-diaryl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carboxylic acid methyl ester **9a** and **9b** with 2-methoxy-1-phenylethanone (**10**) under alkaline conditions (Scheme 1). After usual workup, pure compounds were isolated as 5-cyano/methoxycarbonyl-3-methoxy-6-methylsulfanyl-1,2,4-

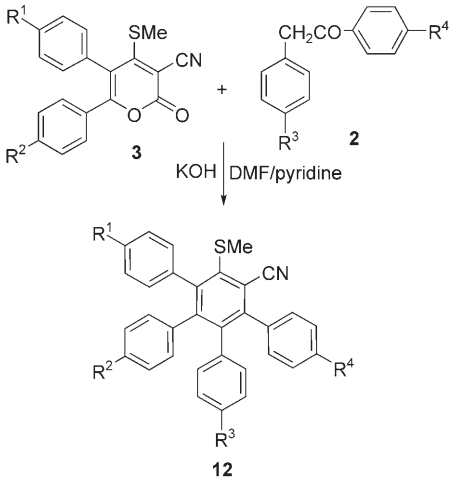


Scheme 1. Synthesis of 1,2,4-triarylbenzenes.

triarylbenzenes **11a–d** in moderate yields. The reaction proceeded by enolate addition of 2-methoxy-1-phenylethanone to lactone **3** or **9**, followed by intramolecular cyclization and decarboxylation to furnish the 1,2,4-triarylbenzenes.

Finally, the synthesis of 1,2,3,4-tetraarylbenzenes was accomplished by stirring a mixture of functionalized deoxybenzoin **2** with 5,6-diaryl-2*H*-pyran-2-one **3** in the presence of KOH in dry DMF at room temperature (Table 3). The reaction was monitored by TLC, which showed an intense blue spot when exposed to short-wave UV radiation at 254 nm. After completion of reaction, the reaction mixture was poured into iced water and neutralized with dilute HCl. The crude product thus obtained was purified by passing through neutral alumina. The purified compound was isolated in 29% yield and characterized as 1,2-diaryl-3-(4′-methoxyphenyl)-4-(4″-methoxyphenyl)-5-cyano-6-methylsulfanylbenzene **12c** by spectroscopic analysis.

Table 3. Synthesis of 1,2,3,4-triarylbenzenes.



12

12	R^1	R^2	R^3	R^4	Yield [%]
a	H	H	H	H	60
b	H	H	H	Cl	58
c	H	H	OMe	OMe	66
d	H	OMe	OMe	OMe	61
e	OMe	OMe	H	Cl	59
f	OMe	OMe	H	H	63
g	OMe	OMe	OMe	OMe	69

To achieve higher yields of the 1,2,3,4-tetraarylbenzenes, a series of optimization studies for **12c** was carried out by varying the reaction conditions and the inorganic bases (e.g., NaH, KOH, K_2CO_3, lithium diisopropylamide (LDA), *t*BuOK). Only KOH and *t*BuOK in various solvents resulted in the formation of 1,2,3,4-tetraarylbenzenes, the rest of the bases were found to be unsuitable. The optimization results are summarized in Table 4.

Interestingly, the KOH/pyridine combination was found to be the best conditions observed for the preparation of 1,2,3,4-tetraarylbenzenes (Table 4, entry 3; 66% yield). Apart from pyridine, the other solvents resulted in a mixture of side products. In the case of pyridine, no side product was obtained, and the 1,2,3,4-tetraarylbenzene was the sole product. A series of 1,2,3,4-tetraarylbenzenes **12a–g** was prepared in 58–69% yields by stirring a mixture of substituted 5,6-diaryl-2*H*-pyran-2-ones **3a**, **3b**, and **3d** with functionalized deoxybenzoins **2** in the presence of KOH in pyridine (Table 3). All the synthesized compounds were characterized by spectroscopic analysis. Notably, these arylated benzenes were prepared in just two steps through easily accessible precursors. This methodology is highly simple and economical compared to the palladium-catalyzed classical approaches used today.

Table 4. Various reaction conditions for the synthesis of 1,2,3,4-tetraarylbenzene **12c**.

Entry	Base[a]	Solvent	*T*	*t* [h]	Yield [%]
1	KOH	DMF	RT	5	29
2	KOH	DMSO	RT	6	20
3	KOH	pyridine	reflux	40	66[b]
4	KOH	toluene	reflux	20	17
5	KOH	fluorobenzene	reflux	40	0
6	*t*BuOK	THF	reflux	30	19

[a] 1.2 Equivalents of base was used in all the reactions. [b] Yield of isolated product is reported by considering the total consumption of **3**.

X-ray Crystal-Structure Analysis

To study the conformational arrangements of the peripheral rings of the polyarylbenzenes, which was the subject of several studies,[17c,e,32] a compound from the series of 1,2-diaryl- and 1,2,3,4-tetraarylbenzenes was crystallized for X-ray structural studies. Diffraction-quality crystals of **4e** and **12c** were obtained by slow evaporation at room temperature. The conformations of **4e** and **12c** together with arbitrary numbering are shown as ORTEP diagrams in Figure 1, which indicates a propeller-like conformation for the peripheral aryl rings with respect to the central benzene ring. The selected torsion angles and mean plane angles between the central benzene and peripheral aryl rings of **4e** and **12c** are shown in Table 5.

The structural analysis[33] of compound **4e** revealed that the average mean plane angle for the twist of the phenyl rings from the plane of the central benzene ring was 59.34°. The crystal packing of **4e** showed a soft C−H···π interaction involving C21−H21B and the centroid (Cg) of the central benzene ring of another molecule (symmetry code: x, $-1+y$, z) with parameters H21B···Cg (ring C) 2.88 Å, C21···Cg (ring C) 3.836(4) Å, C21−H21B···Cg (ring C) 170°. The X-ray structure further revealed the presence of a network of strong intermolecular H-bonding N1−H1B···O2 with H-bonding parameters N1−H1B···O2 (x, y, $-1+z$), H1B···O2 2.39 Å, N1···O2 3.020 (3) Å, and N1−H1B−O2 131°, and C21−H21C···N3 with H-bonding parameters C21−H21C···N3 ($1-x$, $-y$, $1-z$), H21C···N3 2.57 Å, C21···N3 3.495(6) Å, C21−H21C−N3 161°.

Similarly, the X-ray structure analysis[33] of compound **12c** showed that the dihedral angles between the peripheral and

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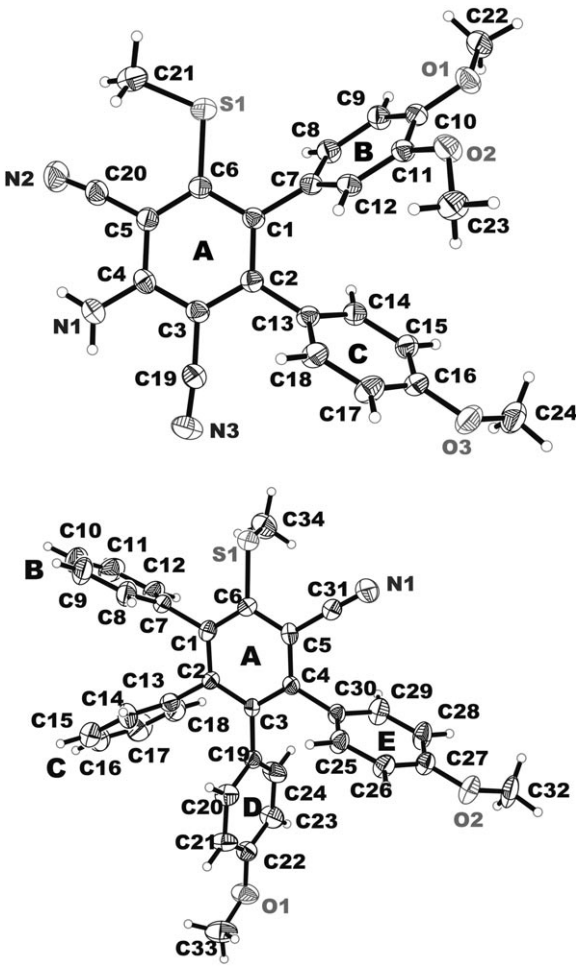

Figure 1. ORTEP diagrams of 1,2-diarylbenzene **4e** (top) and 1,2,3,4-tetraarylbenzene **12c** (bottom) with arbitrary numbering. Thermal ellipsoids are drawn at the 50% probability level. The central ring is marked as ring A and the peripheral rings are marked consecutively as rings B, C, D, and E.

Table 5. Selected torsion and twist angles [°] for **4e** and **12c**.

	Atoms	Torsion angles	Mean plane (twist) angle
4e	C6–C1–C7–C8	–59.5(4)	Ring A–Ring B 57.3(1)
	C1–C2–C13–C14	–59.6(4)	Ring A–Ring C 61.3(1)
12c	C6–C1–C7–C8	–80.8(6)	Ring A–Ring B 79.6(2)
	C1–C2–C13–C14	–79.7(7)	Ring A–Ring C 79.7(1)
	C2–C3–C19–C20	–74.9(6)	Ring A–Ring D 78.9(2)
	C3–C4–C25–C26	–83.2(7)	Ring A–Ring E 80.4(1)

central benzene rings ranges from 75° to 83°. The average mean plane angle of the phenyl rings (rings B, C, D, E) from the plane of the central benzene ring was found to be 79.7°, which shows that the peripheral rings are arranged nearly orthogonal to the central benzene ring, which was found to be about 15° higher than hexaarylbenzene. As a consequence, the four π frameworks are arranged in a propeller-like fashion. The crystal packing of **12c** showed C–H···π interactions involving C17–H17 and the centroid of another benzene molecule (symmetry code: $^1/_2-x$, $1-y$, $-^1/_2+z$) with parameters H17···Cg (ring B) 2.99 Å, C17···Cg (ring B) 3.602(6) Å, C17–H17···Cg (ring B) 125°. Interestingly, the crystal-structure analysis of **12c** revealed N···π interactions (face lone pair–π interactions) (Figure 2).

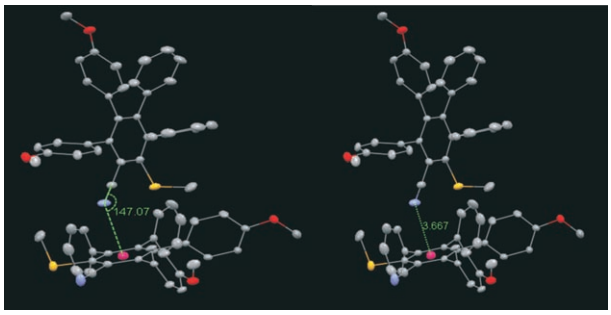

Figure 2. Crystal-packing ellipsoid diagram of **12c** showing the N···π interaction with a neighboring molecule. The sp-hybidized nitrogen atom of the cyano group (N1) interacts directly with the face of the central benzene ring of another molecule with a C–N···benzene centroid distance of 3.668 Å (parameters C31–N1···Cg (ring A) 3.6675 Å, CN1–Cg (ring A) 147°; symmetry code: $-^1/_2+x$, $^1/_2-y$, $2-z$). Atoms are colored: carbon = off-white, oxygen = red, nitrogen = blue, sulfur = yellow.

There are several reports on C–H···π,[34] N–H···π,[35] S···π,[36] and O···π (lone pair–π)[37] interactions, but little attention has been focused on describing N···π interactions.[38] A critical Cambridge Structural Database (CSD) search (ConQuest 1.8) on such N···π interactions (Figure 3) revealed that in most of the cases, the nonbonded distances were greater than the van der Waals summation of N and π contact (3.3 Å). In approximately 150 hits, the observed range for N···π interactions was found to be 2.9–4.1 Å with no selectivity in directionality, and most of the interactions were angled close to 125°. The crystal packing of **12c** (Figure 4) revealed that the lone-pair electrons of the sp-hybridized nitrogen atom of the cyano group interacts with the

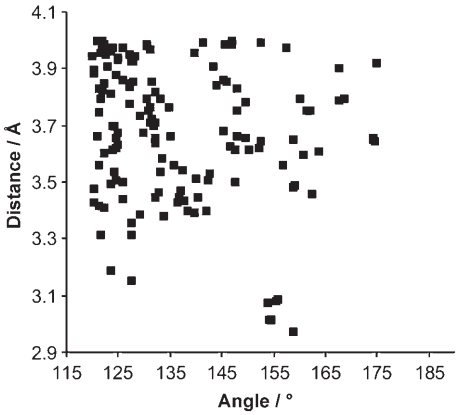

Figure 3. Scatter plot showing N···π interactions. Each black square represents a hit obtained by the CSD search on N···π interactions.

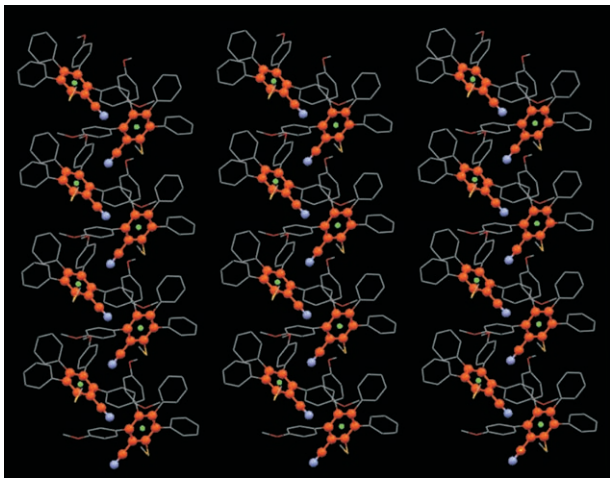

Figure 4. Crystal-packing diagram of **12c** showing N···π interactions between molecules related by a two-fold screw axis running in the direction of the *a* axis. The dihedral angle between the central benzene ring and a neighboring central benzene ring is 70°. Central benzene rings are colored (carbon = orange, nitrogen = blue, centroid = green) for clarity. Hydrogen atoms are omitted for clarity.

face of the central benzene ring at a distance of 3.667 Å with an angle of 147°, thus showing N···π interaction between molecules related by a two-fold screw axis running in the direction of the *a* axis.

The mean plane angle between a central benzene ring and the neighboring central benzene ring below was found to be 70°. The cyano group containing central benzene rings are colored (carbon = orange, nitrogen = blue, centroid = green) for clarity. It is interesting that the repetition of the N···π interaction around the axis of the 1,2,3,4-tetraarylbenzene **12c** forces the molecule into a helix-type packing (Figure 4). In the crystal lattice of **12c**, these helices are connected with each other through H···H intermolecular short contacts.

Conclusions

In summary, we have demonstrated a new synthetic approach for preparing functionally crowded 1,2-diaryl-, 1,2,3- and 1,2,4-triaryl-, and 1,2,3,4-tetraarylbenzenes from ketene-*S,S*-acetals with readily available substrates in just two steps in good to excellent yields. This methodology has several advantages over classical metal-assisted aryl–aryl coupling reactions: 1) it is a highly simple reaction process, 2) it has the flexibility of introducing electron-donor or -acceptor groups even at sterically demanding *ortho*-positions, 3) it does not require expensive organometallic reagents or catalysts, 4) it is a versatile approach for generating molecular diversity, and 5) it gives a high yield of aromatic compounds. X-ray structural analysis of 1,2,3,4-tetraarylbenzene **12c** revealed an N···π interaction in which the lone-pair electrons of the sp-hybridized nitrogen atom interacts with the face of the central benzene ring of a neighboring molecule with a distance of 3.668 Å.

Experimental Section

General

Melting points were determined on a Büchi-530 apparatus in an open capillary and are uncorrected. The reagent-grade reaction solvent DMF was further purified and dried according to the literature procedure. TLC was performed on precoated silica-gel plastic plates and visualized by UV irradiation. IR spectra of solid samples were run as KBr pellets on a Perkin–Elmer AC-1 instrument. ^{1}H NMR spectra were recorded at 200 MHz (Bruker WM-200) in $CDCl_3$ with tetramethylsilane as internal reference. Chemical shifts δ and coupling constants J are reported in ppm and Hz, respectively. Mass spectra were collected at 70 eV on a Jeol JMS-300 spectrometer.

Syntheses

General procedure for the synthesis **1**: Methyl cyanoacetate (35.2 mL, 0.4 mol) was added dropwise to an ice-chilled solution of sodium hydride (10.08 g, 60% oil suspension, 0.42 mol) in THF over a period of 15 min. After complete addition of methyl cyanoacetate, the resulting white semisolid material was vigorously stirred for another 15 min. Carbon disulfide (25.33 mL, 0.4 mol) was added dropwise to this solution while the mixture was kept below 20 °C. The reaction mixture slowly changed from white semisolid to yellow liquid. Methyl iodide (62.55 mL, 1 mol) was added dropwise to the stirred solution over a period of 30 min. After the mixture was stirred for another 15 min at room temperature, THF was removed under reduced pressure. A small amount of crushed ice was added to consume unreacted NaH, and then the residue was poured into ice-cold water with constant stirring. The white crystalline compound was filtered, washed with cold water, dried, and recrystallized with ethyl acetate/hexane (1:4) to give **1** (72.54 g, 89.33%) as white needles. M.p.: 52 °C.

General procedure for the synthesis of **3a–f**: A mixture of **1** (10 mmol), deoxybenzoin (11 mmol), and powdered KOH (12 mmol) in dry DMSO (50 mL) was stirred at room temperature for 10–14 h. After completion of reaction, the mixture was poured into iced water with constant stirring. The precipitate thus obtained was filtered and purified on a silica-gel column with chloroform as eluent.

3a: White solid; m.p.: 160–162 °C; IR (KBr): $\tilde{\nu}$ = 1725 (CO), 2221 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.85 (s, 3H, SCH_3), 7.15–7.23 (m, 6H, ArH), 7.29–7.41 ppm (m, 4H, ArH); MS (FAB): m/z = 320 $[M+1]^+$.

3b: Yellow solid; m.p.: 184–186 °C ; IR (KBr): $\tilde{\nu}$ = 1713 (CO), 2220 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3+CCl_4$): δ = 2.86 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 6.69 (d, J = 9.0 Hz, 2H, ArH), 7.08–7.25 ppm (m, 7H, ArH); MS (FAB): m/z = 350 $[M+1]^+$.

3c: Yellow solid; m.p.: 176–177 °C; IR (KBr): $\tilde{\nu}$ = 1727 (CO), 2219 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3+CCl_4$): δ = 2.85 (s, 3H, SCH_3), 3.60 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.20 (s, 1H, ArH), 6.32 (d, J = 8.4 Hz, 1H, ArH), 6.88–7.07 ppm (m, 5H, ArH); MS (FAB): m/z = 398 $[M+1]^+$.

3d: Yellow solid; m.p.: 176–177 °C; IR (KBr): $\tilde{\nu}$ = 1718 (CO), 2217 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.83 (s, 3H, SCH_3), 3.77 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.70 (d, J = 8.8 Hz, 2H, ArH), 6.92 (d, J = 8.8 Hz, 2H, ArH), 7.08 (d, J = 8.8 Hz, 2H, ArH), 7.22 ppm (d, J = 8.8 Hz, 2H, ArH); MS (FAB): m/z = 380 $[M+1]^+$.

3e: Yellow solid; m.p.: 181–182 °C; IR (KBr): $\tilde{\nu}$ = 1721 (CO), 2219 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.84 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.66–6.75 (m, 4H, ArH), 6.89 (d, J = 8.2 Hz, 1H, ArH), 7.25 ppm (d, J = 8.2 Hz, 2H, ArH); MS (FAB): m/z = 410 $[M+1]^+$.

3f: Yellow solid; m.p.: 158–160 °C; IR (KBr): $\tilde{\nu}$ = 1713 (CO), 2220 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.86 (s, 3H, SCH_3), 3.77 (s, 3H, OCH_3), 6.66 (d, J = 9.0 Hz, 2H, ArH), 7.04–7.20 ppm (m, 6H, ArH); MS (FAB): m/z = 368 $[M+1]^+$.

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General procedure for the synthesis of **4a–f**: A mixture of **3a–f** (1 mmol), malononitrile (1 mmol), and powdered KOH (1.2 mmol) in dry DMF (5 mL) was stirred at room temperature for 6–8 h. At the end of the reaction, the mixture was poured into iced water with vigorous stirring and finally neutralized with dilute HCl. The solid thus obtained was filtered and purified on a neutral alumina column with chloroform/hexane (1:4) as eluent.

4a: White solid; m.p.: 198–200 °C; IR (KBr): $\tilde{\nu}$ = 2219 (CN), 3353, 3468 cm^{-1} (NH_2); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.27 (s, 3H, SCH_3), 5.31 (br s, 2H, NH_2), 6.93–6.96 (m, 2H, ArH), 7.00–7.04 (m, 2H, ArH), 7.15–7.22 ppm (m, 6H, ArH); ^{13}C (200 MHz, $CDCl_3$): δ = 19.7 (SCH_3), 97.9, 100.8, 115.8 (CN), 115.9 (CN), 127.9, 128.2, 128.4, 128.9, 129.6, 131.3, 135.2, 137.2, 147.7, 150.0, 152.0 ppm; MS (FAB): m/z = 342 $[M+1]^+$.

4b: White solid; m.p.: 240–242 °C; IR (KBr): $\tilde{\nu}$ = 2214 (CN), 3348, 3464 cm^{-1} (NH_2); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.26 (s, 3H, SCH_3), 3.74 (s, 3H, OCH_3), 5.29 (br s, 2H, NH_2), 6.71 (d, J = 8.6 Hz, 2H, ArH), 6.94 (d, J = 8.2 Hz, 4H, ArH), 7.17–7.20 ppm (m, 3H, ArH); ^{13}C (200 MHz, $CDCl_3$): δ = 19.6 (SCH_3), 55.5 (OCH_3), 98.2, 100.6, 113.9, 115.8 (CN), 116.1 (CN), 127.8, 128.3, 129.3, 131.0, 131.3, 135.5, 137.4, 149.9, 152.0, 160.0 ppm; MS (FAB): m/z = 372 $[M+1]^+$.

4c: White solid; m.p.: 238–240 °C ; IR (KBr): $\tilde{\nu}$ = 2214 (CN), 3348, 3464 cm^{-1} (NH_2); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.28 (s, 3H, SCH_3), 3.64 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.22 (br s, 2H, NH_2), 6.31 (d, J = 8.0 Hz, 1H, ArH), 6.71 (d, J = 8.0 Hz, 1H, ArH), 6.84–6.90 (m, 4H, ArH), 7.17 ppm (d, J = 8.0 Hz, 1H, ArH); MS (FAB): m/z = 420 $[M+1]^+$.

4d: White solid; m.p.: 220–222 °C; IR (KBr): $\tilde{\nu}$ = 2209 (CN), 3347, 3423 cm^{-1} (NH_2); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.27 (s, 3H, SCH_3), 3.76 (s, 6H, $2OCH_3$), 5.25 (br s, 2H, NH_2), 6.69–6.76 (m, 4H, ArH), 6.85 (d, J = 8.8 Hz, 2H, ArH), 6.95 ppm (d, J = 8.8 Hz, 2H, ArH); MS (FAB): m/z = 402 $[M+1]^+$.

4e: White solid; m.p.: 202–204 °C; IR (KBr): $\tilde{\nu}$ = 2216 (CN), 3350, 3466 cm^{-1} (NH_2); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.30 (s, 3H, SCH_3), 3.65 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.27 (br s, 2H, NH_2), 6.38 (s, 1H, ArH), 6.54 (d, J = 8.0 Hz, 1H, ArH), 6.69–6.76 (m, 3H, ArH), 6.92–6.96 ppm (m, 2H, ArH); MS (FAB): m/z = 432 $[M+1]^+$.

4f: White solid; m.p.: 224–226 °C ; IR (KBr): $\tilde{\nu}$ = 2219 (CN), 3349, 3470 cm^{-1} (NH_2); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.29 (s, 3H, SCH_3), 3.76 (s, 3H, OCH_3), 5.29 (br s, 2H, NH_2), 6.74 (d, J = 8.6 Hz, 2H, ArH), 6.88–6.92 ppm (m, 6H, ArH); MS (FAB): m/z = 390 $[M+1]^+$.

8a: Yellow crystalline solid; m.p.: 188–189 °C; IR (KBr): $\tilde{\nu}$ = 2218 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.64–1.68 (m, 2H, CH_2), 1.78–1.84 (m, 4H, 2 × CH_2), 2.28 (s, 3H, CH_3), 3.25–3.30 (m, 4H, 2 × CH_2), 3.76 (s, 3H, OCH_3), 6.25 (dd, J = 9.2, 2.6 Hz, 1H, ArH), 6.58 (d, J = 9.2 Hz, 1H, ArH), 6.73 (d, J = 2.6 Hz, 1H, ArH), 6.85–7.04 (m, 7H, ArH), 7.17–7.21 ppm (m, 3H, ArH); MS (FAB): m/z = 475 $[M+1]^+$.

8b:Yellow crystalline solid; m.p.: 211–212 °C; IR (KBr): $\tilde{\nu}$ = 2218 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.61–1.64 (m, 2H, CH_2), 1.79–1.84 (m, 4H, 2 × CH_2), 3.24–3.32 (m, 4H, 2 × CH_2), 3.77 (s, 3H, OCH_3), 6.26 (dd, J = 9.2, 2.6 Hz, 1H, ArH), 6.56–6.65 (m, 2H, ArH), 6.73 (d, J = 2.6 Hz, 1H, ArH), 6.80–6.86 (m, 1H, ArH), 6.95–7.01 (m, 1H, ArH), 7.10–7.16 (m 2H, ArH), 7.16–7.22 (m, 2H, ArH), 7.27–7.34 ppm (m, 2H, ArH); MS (FAB): m/z = 468 $[M+1]^+$.

8c: White solid; m.p.: 128–129 °C; IR (KBr): $\tilde{\nu}$ = 2217 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.59–1.63 (m, 2H, CH_2), 1.79–1.84 (m, 4H, 2 × CH_2), 3.20–3.27 (m, 4H, 2 × CH_2), 3.68 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.49 (d, J = 8.8 Hz, 2H, ArH), 6.56 (d, J = 8.8 Hz, 2H, ArH), 6.73 (d, J = 8.8 Hz, 2H, ArH), 6.87–7.08 (m, 5H, ArH), 7.27–7.33 ppm (m, 2H, ArH); MS (FAB): m/z = 492 $[M+1]^+$.

8d: White solid; m.p.: 170–171 °C; IR (KBr): $\tilde{\nu}$ = 2215 cm^{-1} (CN); ^1H NMR(200 MHz, $CDCl_3$): δ = 1.58–1.64 (m, 2H, CH_2), 1.77–1.83 (m, 4H, 2 × CH_2), 3.22–3.31 (m, 4H, 2 × CH_2), 3.61 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.43 (d, J = 8.7 Hz, 2H, ArH), 6.65 (d, J = 8.7 Hz, 2H, ArH) 6.74 (d, J = 8.7 Hz, 2H, ArH), 6.98–7.11 (m, 4H, ArH), 7.41–7.53 (m, 3H, ArH), 7.67–7.74 ppm (m, 3H, ArH); MS (FAB): m/z = 524 $[M+1]^+$.

9a: White solid; m.p.: 162–164 °C; IR (KBr): $\tilde{\nu}$ = 1693 (CO), 1722 cm^{-1}(CO); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.25 (s, 3H, SCH_3), 3.93 (s, 3H, OCH_3), 7.10–7.35 ppm (m, 10H, ArH); MS (FAB): m/z = 353 $[M+1]^+$.

9b: Yellow solid; m.p.: 218–220 °C ; IR (KBr): $\tilde{\nu}$ = 1695 (CO), 1737 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.27 (s, 3H, SCH_3), 3.76 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.69 (d, J = 8.8 Hz, 2H, ArH), 6.90 (d, J = 8.8 Hz, 2H, ArH), 7.11 (d, J = 8.8 Hz, 2H, ArH), 7.20 ppm (d, J = 8.8 Hz, 2H, ArH); MS (FAB): m/z = 413 $[M+1]^+$.

11a: White solid; m.p.: 186–188 °C; ^{1}IR (KBr): $\tilde{\nu}$ = 2222 cm^{-1} (CN); H NMR (200 MHz, $CDCl_3$): δ = 2.23 (s, 3H, SCH_3), 3.00 (s, 3H, OCH_3), 7.00–7.07 (m, 4H, ArH), 7.12–7.22 (m, 6H, ArH), 7.43–7.60 ppm (m, 5H, ArH); MS (FAB): m/z = 408 $[M+1]^+$.

11b: White solid; m.p.: 226–228 °C; IR (KBr): $\tilde{\nu}$ = 2221 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.21 (s, 3H, SCH_3), 2.98 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.66–6.79 (m, 4H, ArH), 6.96 (d, J = 8.6 Hz, 4H, ArH), 7.42–7.55 ppm (m, 5H, ArH); MS (FAB): m/z = 468 $[M+1]^+$.

11c: White solid; m.p.: 188–190 °C; IR (KBr): $\tilde{\nu}$ = 1731 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.00 (s, 3H, SCH_3), 2.99 (s, 3H, OCH_3), 3.62 (s, 3H, $COOCH_3$), 7.05–7.16 (m, 9H, ArH), 7.36–7.49 ppm (m, 6H, ArH); MS (FAB): m/z = 440 $[M+1]^+$.

11d: White solid; m.p.: 196–198 °C; IR (KBr): 1731 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.98 (s, 3H, SCH_3), 2.98 (s, 3H, OCH_3), 3.61 (s, 3H, $COOCH_3$), 3.74 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.65–6.76 (m, 4H, ArH), 6.92–7.05 (m, 4H, ArH), 7.36–7.47 ppm (m, 5H, ArH); MS (FAB): m/z = 500 $[M]^+$.

12a: White solid; m.p.: 216–218 °C; IR (KBr): $\tilde{\nu}$ = 2224 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.34 (s, 3H, SCH_3), 6.64–6.67 (m, 5H, ArH), 6.81–6.90 (m, 6H, ArH), 7.01–7.25 ppm (m, 9H, ArH); MS (FAB): m/z = 454 $[M+1]^+$.

12b: White solid; m.p.: 248–250 °C; IR (KBr): $\tilde{\nu}$ = 2215 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3H, SCH_3), 6.62–6.80 (m, 3H, ArH), 6.83–6.93 (m, 6H, ArH), 7.00–7.09 (m, 2H, ArH), 7.12–7.35 ppm (m, 8H, ArH); MS (FAB): m/z = 488 $[M+1]^+$.

12c: White solid; m.p.: 210–212 °C; IR (KBr): $\tilde{\nu}$ = 2215 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3H, SCH_3), 3.61 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.42–6.46 (m, 2H, ArH), 6.58–6.86 (m, 10H, ArH), 7.05–7.16 ppm (m, 6H, ArH); MS (FAB): m/z = 514 $[M+1]^+$.

12d: White solid; m.p.: 162–164 °C; IR (KBr): $\tilde{\nu}$ = 2214 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3H, SCH_3), 3.61 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.40 (d, J = 8.6 Hz, 2H, ArH), 6.44 (d, J = 8.6 Hz, 2H, ArH), 6.56–6.63 (m, 4H, ArH), 6.76 (d, J = 8.6 Hz, 2H, ArH), 7.04–7.10 (m, 4H, ArH), 7.17–7.20 ppm (m, 3H, ArH); MS (FAB): m/z = 544 $[M+1]^+$.

12e: White solid; m.p.: 222–224 °C; IR (KBr): $\tilde{\nu}$ = 2214 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3H, SCH_3), 3.61 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.41 (d, J = 8.4 Hz, 2H, ArH), 6.58 (d, J = 8.4 Hz, 2H, ArH), 6.68–6.76 (m, 4H, ArH), 6.90–7.98 (m, 5H, ArH), 7.09 (d, J = 8.4 Hz, 2H, ArH), 7.20 ppm (d, J = 8.4 Hz, 2H, ArH); MS (FAB): m/z = 548 $[M+1]^+$.

12f: White solid; m.p.: 202–204 °C; IR (KBr): $\tilde{\nu}$ = 2215 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3H, SCH_3), 3.61 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.42 (d, J = 8.6 Hz, 2H, ArH), 6.62 (d, J = 8.6 Hz, 2H, ArH), 6.69–6.87 (m, 8H, ArH), 7.02–7.18 ppm (m, 6H, ArH); MS (FAB): m/z = 514 $[M+1]^+$.

12g: White solid; m.p.: 218–220 °C; IR (KBr): $\tilde{\nu}$ = 2219 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3H, SCH_3), 3.63 (s, 6H, 2 × OCH_3), 3.76 (s, 6H, 2 × OCH_3), 6.39–6.45 (m, 4H, ArH), 6.56–6.62 (m, 4H, ArH), 6.70–6.78 (m, 4H, ArH), 6.95 (d, J = 8.6 Hz, 2H, ArH) 7.07 ppm (d, J = 8.6 Hz, 2H, ArH); ^{13}C (200 MHz, $CDCl_3$): δ = 20.2 (SCH_3), 55.3 (OCH_3), 55.5 (OCH_3), 112.9, 113.0, 113.3, 113.8, 118.1 (CN), 118.8, 130.8, 131.3, 131.6, 131.9, 132.0, 132.3,139.8, 142.4, 146.2, 146.5, 146.8, 157.9, 158.6, 159.3 ppm ; MS (FAB): m/z = 574 $[M+1]^+$.

X-ray Structure Determination

Unit-cell determination and intensity-data collection ($2\theta = 50°$) was performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions were performed by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS (Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA, 1996), SHELXTL-NT (Bruker AXS Inc.: Madison, Wisconsin, USA, 1997), PLATON (A. L. Spek, Utrecht University, Utrecht, Netherlands, 2004), MERCURY (Version 1.4). CCDC-298046 (**4e**) and -298045 (**12c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk) or at www.ccdc.cam.uk/conts/retrieving.html.

Crystal data of **4e**: $C_{24}H_{21}N_3O_3S$, $M_r = 431.5$, triclinic, $P\bar{1}$, $a = 10.228(1)$, $b = 10.325(1)$, $c = 11.575(2)$ Å, $\alpha = 101.05(1)$, $\beta = 109.11(10)$, $\gamma = 102.63(1)°$, $V = 1080.1(2)$ Å^3, $Z = 2$, $\rho_{cald} = 1.327$ g cm^{-3}, μ ($Mo_{K\alpha}$) = 0.181 mm^{-1}, $F(000) = 452$, yellow, rectangular block, size = $0.23 \times 0.20 \times 0.10$ mm^3, 4374 reflections measured ($R_{int} = 0.0266$), 3717 unique, $wR_2 = 0.1415$ for all data, conventional $R = 0.0487$ [$(\Delta/\sigma)_{max} = 000$] on 2064 reflections with $I > 2\sigma(I)$, $S = 1.021$ for all data and 284 parameters.

Crystal data of **12c**: $C_{34}H_{27}NO_2S$, $M_r = 513.63$, orthorhombic, $P2_12_12_1$, $a = 8.787$ (1), $b = 17.177(2)$, $c = 18.374(2)$ Å, $V = 2773.3(5)$ Å^3, $Z = 4$, $\rho_{cald} = 1.23$ g cm^{-3}, μ ($Mo_{K\alpha}$) = 0.148 mm^{-1}, $F(000) = 1080$, colorless block, crystal dimensions $0.23 \times 0.23 \times 0.10$ mm^3, 3579 reflections measured ($R_{int} = 0.0385$), 3374 unique, $wR2 = 0.1184$ for all data, $R = 0.0504$ [$(\Delta/\sigma)_{max} = 000$] on 1590 reflections with $I > 2\sigma(I)$, $S = 0.958$ for all data and 346 parameters.

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