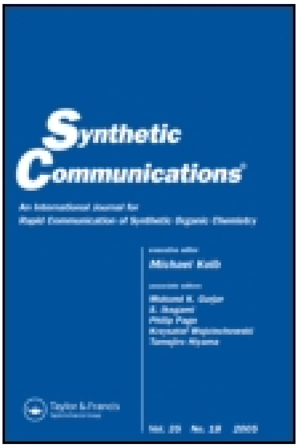

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
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Efficient One-Step Synthesis of C_3-Symmetrical Benzenoid Compounds Mediated by $SOCl_2$/EtOH

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Accepted author version posted online: 01 Feb 2012.Version of record first published: 20 Aug 2012.

To cite this article: Sanhu Zhao, Lina Kang, Haixia Ge, Feifei Yang, Chenlu Wang, Chang Li, Qiang Wang & Minggen Zhao (2012): Efficient One-Step Synthesis of C_3-Symmetrical Benzenoid Compounds Mediated by $SOCl_2$/EtOH, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:24, 3569-3578

To link to this article: http://dx.doi.org/10.1080/00397911.2011.585731

Synthetic Communications®, 42: 3569–3578, 2012
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.585731

EFFICIENT ONE-STEP SYNTHESIS OF *C*3-SYMMETRICAL BENZENOID COMPOUNDS MEDIATED BY $SOCl_2$/EtOH

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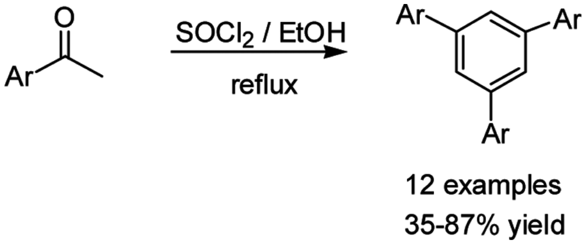
GRAPHICAL ABSTRACT



Abstract *An efficient one-step synthesis of branched functionalized benzenoid compounds from aryl methyl ketones mediated by $SOCl_2$/EtOH is described; some novel* C_3*-symmetrical molecules were prepared with satisfactory yields. The method enjoys short reaction time and simple operation, and avoids use of organometallic reagents.*

Keywords Aryl methyl ketone; carbazole; C_3-symmetrical molecules; cyclotrimerization; thionyl chloride

INTRODUCTION

In recent years, C_3-symmetrical molecules including polycyclic aromatic hydrocarbons,[1] dendrimers,[2] and star polymers[3] have attracted considerable attention because of their potential applications in electronics, physics, biology, and medical diagnosis.[4] 1,3,5-Trisubstituted benzenes, which have a C_3-symmetrical structure, are versatile organic intermediates for the synthesis of fullerene precursors, electroluminescent materials, sensitizers for photographic processes, and conjugated star polyaromatics.[5] As a result, a variety of methodologies have been developed to design and synthesize 1,3,5-trisubstituted benzenes. To our knowledge, there are three routes to access the product. One is transition metal–catalyzed [2 + 2 + 2]

Received February 8, 2011.

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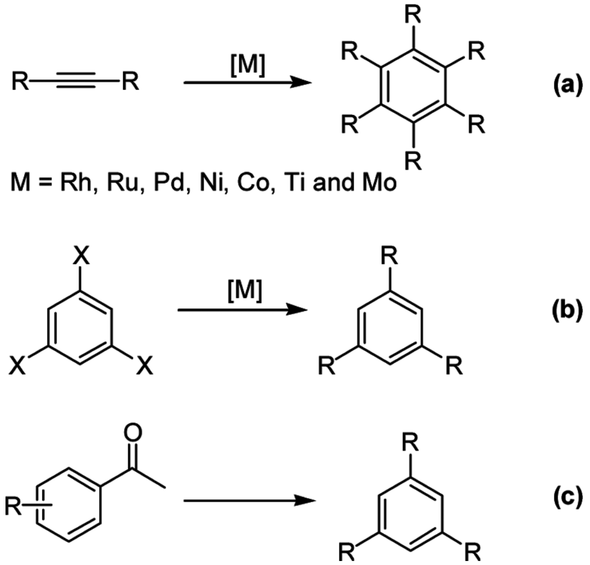
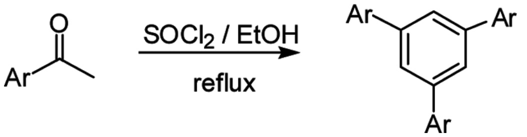


Scheme 1. Three pathways to access 1,3,5-trisubstituted benzenes.



Scheme 2. Condensation reaction of aryl methyl ketones mediated by $SOCl_2$/EtOH.

cyclotrimerization of alkynes (path a, Scheme 1).[6] The other route is metal-catalyzed cross-coupling reactions between 1,3,5-trihalobenzenes with organometallic partners (path b, Scheme 1).[7] The methodologies mentioned often involve transition metals or noble metals. The need for high catalyst loading in some of these processes results in high economic cost. The presence of heavy transition-metal impurities in the final products also presents a major problem for purification.

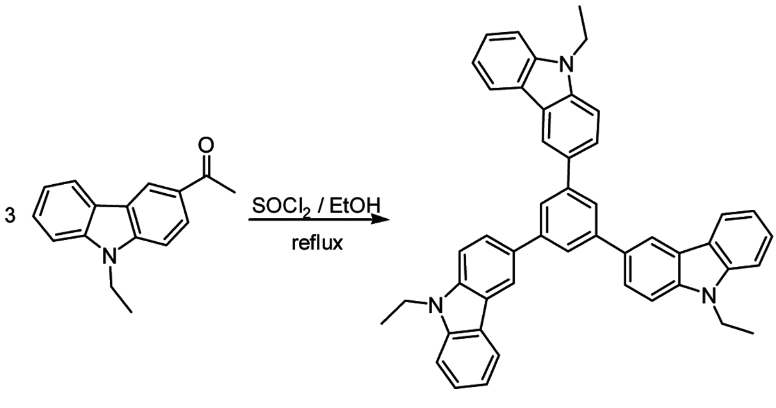
Compared with the former routes, the third route, synthesis of 1,3,5-triarylbenzenes from monoacetylaromatic compounds, has been regarded as the most simple and reliable way (path c, Scheme 1). Many catalysts such as hydrochloric acid,[8] sodium or potassium pyrosulfate in H_2SO_4,[9] aniline hydrochloride,[10] TsOH,[11] amberlyst-15,[12] titanium tetrachloride ($TiCl_4$),[13] $SiCl_4$,[14] $SmCl_3$,[15] $CuCl_2$,[16] $SiCl_4$–methanol,[17] and Cp_2ZrCl_2[18] have been reported in the literature. However, except for a few examples, most of these procedures suffer from drawbacks such as use of precious metal catalysts, long reaction times, or harsh operating conditions. Herein, we report a novel and facile method to access the 1,3,5-trisubstituted benzenes from aryl methyl ketones mediated by $SOCl_2$/EtOH (Scheme 2).

RESULTS AND DISCUSSION

Thionyl chloride is the most attractive reagent for the chlorination of alcohols because of the short reaction time, low reaction temperature, and low price.[19] Recently, Chmielewski et al. reported utilization of thionyl chloride as a chlorination agent to synthesize 3,6-dichlorocarbazole from carbazole with good yield.[20] Based on this, we applied this method to introduce a chlorine atom at the 6-position of 3-acetyl-9-ethylcarbazole. The reaction was conducted in the presence of thionyl chloride in CH_2Cl_2 at room temperature; however, the corresponding 3-acetyl-9-ethyl-6-chlorocarbazole was not detected. To optimize the reaction conditions and obtain the object product, some reagents such as tetrahydrofuran (THF), 1,4-dioxane, toluene, and ethanol were employed as reaction solvents. When ethanol was chosen as solvent, following the addition of thionyl chloride and reflux of the reaction mixture, the reaction was detected by thin-layer chromatography (TLC). After 8 h, the reaction mixture was treated with a saturated solution of sodium carbonate and the product was isolated. To our surprise, the ^{1}H NMR and ^{13}C NMR spectram showed that the product was not the intended product. After careful comparison of the Fourier transform infrared (FTIR), ^{1}H NMR, and ^{13}C NMR spectram of the unknown product with the reactant 3-acetyl-9-ethylcarbazole, we noticed that the IR signal (1660 cm^{-1}, -$COCH_3$), the ^{13}C NMR signal (197.64 ppm, 26.57 ppm, -$COCH_3$), and the ^{1}H NMR signal (2.65 ppm, -$COCH_3$) of the reactant 3-acetyl-9-ethylcarbazole apparently disappeared. Thus, we deduced that the reaction's active position may be the acetyl group. To further confirm the structure of the product, the mass spectral (MS) data of the product were measured. According to the experimental results, we presumed that the product was formed from triple condensation of 3-acetyl-9-ethylcarbazole (Scheme 3).

To verify the result, 4-iodoacetophenone was used in this system. To our delight, under the same conditions, the reaction was completed after 1.5 h, and the melt point and the data of ^{1}H NMR and ^{13}C NMR spectram of the product were consistent with 1,3,5-tri-(*p*-iodophenl)-benzene as reported in the literature.[11]

To obtain the best results, the reaction of acetophenone mediated by $SOCl_2$/EtOH was carried out under different reaction conditions. The effect of molar ratio



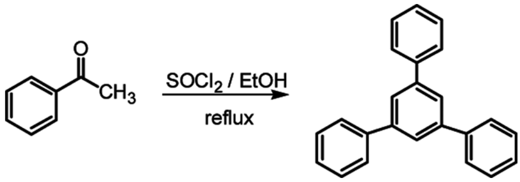
Scheme 3. Triple condensation of 3-acetyl-9-ethylcarbazole.

of reaction reagents and the effect of reaction time were carefully investigated (Table 1). The results indicate that the molar excess of thionyl chloride (1.67 equivalent, Table 1, entry 8) and the controlled reaction time would be more useful to obtain the best yield, Longer reaction times reduce the product yield while increasing the by-product.

To elucidate the role of ethanol in this process, we conducted the reaction of acetophenone with thionyl chloride in ethanol-free CH_2Cl_2. As a result, the conversion (0%, Table 1, entry 1) was gained under this condition. It may seem obvious that ethanol plays an important role in the formation of the cyclotrimerized product.

With the optimized reaction conditions in hand (Table 1, entry 8), various aryl methyl ketones were tested to extend the utility of this reaction. It was found that aryl methyl ketones carrying weak electron-donating groups or weak electron-withdrawing groups could be smoothly converted to the desired products with excellent isolated yields (82–87%, Table 2, entries 1–5). The triple condensation of aryl methyl ketones containing strong electron-donating groups and electron-withdrawing groups afforded 1,3,5-trisubstituted benzenes in poor to moderate isolated yields (35% and 68%, Table 2, entries 6 and 8). This decrease of yields can be attributed to the nature of the substituent group. The strong electron-donating group (–OCH_3) does not favor ethanol addition to the carbonyl (Scheme 4) and the strong electron-withdrawing group (–NO_2) does not favor the oxygen of the carbonyl addition to the thionyl chloride. For aryl methyl ketones carrying an *ortho* substituent (Table 2, entry 9), only trace product was found. The reasons for the yield decrease could be attributed to the steric effect and

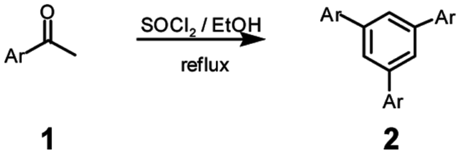
Table 1. Effects of the ratio of $C_6H_5COCH_3/SOCl_2/EtOH$ and reaction time



Entry	$n(C_6H_5COCH_3)/n(SOCl_2)/n(EtOH)$	Time (min)	Yield (%)
1[a]	3:5:0	90	0
2	3:3:6	90	38
3	3:3:9	90	43
4	3:3:12	90	49
5	3:3:15	90	57
6	3:3:18	90	57
7	3:4:15	90	71
8	**3:5:15**	**90**	**87**
9	3:6:15	90	85
10	3:5:15	70	76
11	3:5:15	100	86
12	3:5:15	120	75

[a] The reaction was run with acetophenone (0.075 mol), 25 mL CH_2Cl_2, and 9.1 mL $SOCl_2$ (0.125 mol).

Table 2. $SOCl_2$/EtOH-mediated synthesis of 1,3,5-trisubstituted benzenes from aryl methyl ketones[a, b]



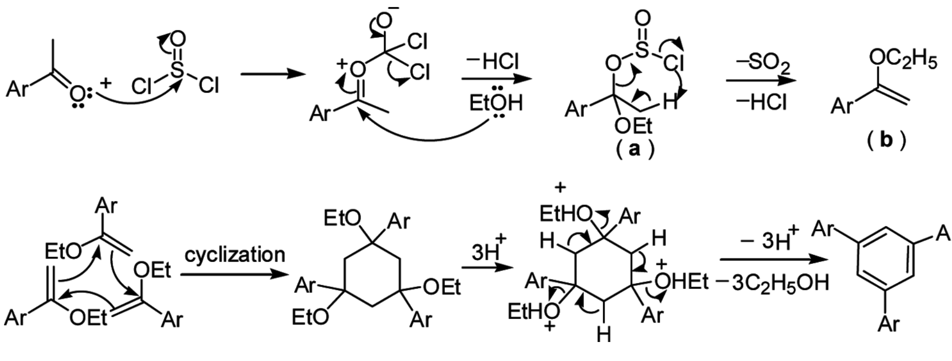
Entry	Ar	2	Time (h)	Yield[c] (%)
1	C_6H_5	**2a**	1.5	87
2	*p*-$CH_3C_6H_5$	**2b**	1.5	84
3	*p*-ClC_6H_5	**2c**	1.5	82
4	*p*-BrC_6H_5	**2d**	1.5	83
5	*p*-IC_6H_5	**2e**	1.5	85
6	*p*-$NO_2C_6H_5$	**2f**	3	35
7	*p*-$NH_2C_6H_5$	**2g**	3	Trace
8	*p*-$CH_3OC_6H_5$	**2h**	3	68
9	*m*-$NO_2C_6H_5$	**2i**	3	Trace
10	9-Ethyl-3-carbazolyl	**2j**	8	42
11	6-*tert*-Butyl-9-ethyl-3-carbazolyl	**2k**	6	47
12	9-Ethyl-6-nitro-3-carbazolyl	**2l**	8	43

[a] The reactions were run with aryl methyl ketone (0.075 mol), 22 mL absolute ethanol, and 9.1 mL $SOCl_2$ (0.125 mol).

[b] The reaction was monitored by thin-layer chromatography (TLC).

[c] Isolated yields.

electronic effect. Recently, Hu and Zhang separately employed the thionyl chloride in this condensation reaction, and the substrates containing strong electron-donating group (–NO_2) delivered poor yield.[21] Zhang reasoned that chalcone formed from 4-nitroacetophenone was insoluble in anhydrous ethanol and further stopped the condensation. Indeed, the solubility of the reactant or intermediates is an important role in the organic reaction; however, this type of condensation reaction may be more similar to benzoin condensation reaction, and the electronic effect and steric effect are probably the most important factors. In a previous report,[17] Elmorsy



Scheme 4. Possible mechanism.

et al. introduced a facile procedure to induce mixed condensation of aryl methyl ketones with the aid of a tetrachlorosilane–ethanol system, and the reaction of 4-nitroacetophenone with acetophenone carried out in pure ethanol afforded the adduct 1-(4-nitrophenyl)-3,5-diphenylbenzene in 85% yield. The result showed that the solubility of 4-nitroacetophenone in ethanol is not the key factor for this type of reaction.

To explore the scope of this reaction, some other heterocyclic compounds containing carbazol units were employed in this reaction (Table 2, entries 11 and 12). To our knowledge, these substrates play an important role in the field of luminescence materials and never have been synthesized by this type of reaction. Interestingly, when 1-(6-*tert*-butyl-9-ethylcarbazol-3-yl)-ethanone and 1-(9-ethyl-6-nitrocarbazol-3-yl)-ethanone were used as starting materials, two novel heterocyclic 1,3,5-trisubstituted benzenes were formed in 47% and 43% yields (Table 2, entries 11 and 12).

A plausible mechanism for the formation of 1,3,5-trisubstituted benzene in the presence of $SOCl_2$/EtOH is depicted in Scheme 4. First, the aryl methyl ketone, $SOCl_2$, and EtOH would react to form chlorosulfite ester (**a**), and subsequent loss of SO_2[22] and HCl from the chlorosulfite ester (**a**) led to the formation of ethyl enol ether (**b**). Then, 1,3,5-triaryl-1,3,5-triethoxy-cyclohexane was formed through cyclization of three monomers (enol ether form). Finally, in the presence of HCl, 1,3,5-triarylbene was given by aromatization via elimination of three ethanol species.

CONCLUSIONS

In summary, we have developed an efficient $SOCl_2$/EtOH-mediated trisannulation and further aromatization of aryl methyl ketones, leading to 1,3,5-trisubstituted benzenes under simple and experimental conditions. Some novel C_3-symmetrical molecules containing cabazole units were synthesized from easily available starting materials via this practical synthetic procedure. As can be seen from the described results, these reactions provide convenient and more efficient methods to prepare highly branched molecules, and novel synthetic pathways have been elaborated.

EXPERIMENTAL

All chemical reagents were obtained from commercial suppliers and used without further purification. Melting points were measured on a WRS-1B digital melting-point meter and are uncorrected. The IR spectra were determined on an FTIR-8400 spectrometer by dispersing samples in KBr disks. ^{1}H NMR and ^{13}C NMR spectra were measured on a DRX300 NMR spectrometer, Bruker ARX400 spectrometer, and Bruker Avance 500-MHz spectrometer using tetramethylsilane (TMS) as an internal standard in $CDCl_3$ or dimethylsulfoxide (DMSO-d_6). Electron impact (EI)–MS were determined with an Agilent 5975N mass spectrometer. The elemental analysis was performed at the Institute of Chemistry, Chinese Academy of Sciences. Flash column chromatography was performed using silica gel (300–400 mesh).

Synthesis of 1,3,5-Trisubstituted Benzenes 2a–l

To a 100-mL, two-necked, round-bottom bottle, 0.075 mol of aryl methyl ketone and 22 mL of absolute ethanol were added. With vigorous stirring, 9.1 mL

(0.125 mol) of $SOCl_2$ was added in a dropwise way over a period of about 30–40 min, and then the reaction mixture was stirred, gently refluxed, and determined by TLC. After completion of the reaction, the reaction mixture was neutralized by saturated Na_2CO_3. The precipitate was collected by filtration, washed with 30 mL H_2O and 30 mL ethanol, and dried in vacuum to yield the almost pure product. The products **2j, 2k**, and **2l** (Table 2, entries 10, 11, and 12) were further purified by column chromatography (PE/EA = 8:1).

1,3,5-Triphenylbenzene (2a)

Light yellow solid; mp 172.3–172.8 °C (lit.[11b] 172 °C). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.71$ (s, 3H), 7.63 (d, $J = 8.0$ Hz, 6H), 7.42–7.39 (t, $J = 7.65$ Hz, 6H), 7.33–7.30 (t, $J = 7.35$ Hz, 3H).

1,3,5-Tri(4-methylphenyl)benzene (2b)

Light yellow solid; mp 177.1–178.4 °C (lit.[8b] 178 °C). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.73$ (s, 3H), 7.62 (d, $J = 8.0$ Hz, 6H), 7.28–7.30 (d, $J = 8.0$ Hz, 6H), 2.44 (s, 9H).

1,3,5-Tri(4-chlorophenyl)benzene (2c)

Light yellow solid; mp 245.8–246.4 °C (lit.[8b] 246 °C). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.70$ (s, 3H), 7.61 (d, $J = 8.5$ Hz, 6H), 7.44 (d, $J = 8.5$ Hz, 6H).

1,3,5-Tri(4-bromophenyl)benzene (2d)

Light yellow solid; mp 261.7–262.5 °C (lit.[12] 260–261 °C). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.61$ (s, 3H), 7.53 (d, $J = 8.55$ Hz, 6H), 7.45 (d, $J = 8.55$ Hz, 6H).

1,3,5-Tri(4-iodophenyl)benzene (2e)

White solid; mp 265.1–265.7 °C (lit.[11a] 265 °C). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.83$ (d, $J = 8.00$ Hz, 6H), 7.71 (s, 3H), 7.42 (d, $J = 8.00$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 141.6$, 140.2, 138.0, 129.1, 124.9, 93.6.

1,3,5-Tri(4-nitrophenyl)benzene (2f)

Light yellow solid; mp 152.7–153.5 °C (lit.[8b] 153 °C). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.3$ (d, $J = 9$ Hz, 2H), 8.1 (d, $J = 9$ Hz, 2H), 7.71 (s, 3H).

1,3,5-Tri(4-methoxyphenyl)benzene (2h)

Light yellow solid; mp 144.2–144.7 °C (lit.[8b] 143 °C). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.65$ (s, 3H), 7.62 (d, $J = 9.0$ Hz, 6H), 6.99 (d, $J = 9$ Hz, 6H), 3.85 (s, 9H).

1,3,5-Tri(9-ethylcarbazol-3-yl)benzene (2j)

Yellow solid; mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.80$ (s, 3H), 8.36 (d, $J = 7.6$ Hz, 3H), 8.17 (s, 3H), 8.08 (t, $J = 8.0$ Hz, 6H), 7.75 (d, $J = 8.0$ Hz, 3H), 7.64 (d, $J = 8.0$ Hz, 3H), 4.62 (d, $J = 6.8$ Hz, 6H), 7.51–7.47 (t, $J = 7.6$ Hz, 3H), 7.29–7.22 (m, 3H), 4.50 (t, $J = 6.8$ Hz, 6H), 1.37 (t, $J = 6.8$ Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 142.44$, 140.03, 138.22, 131.58, 125.87, 125.22, 123.58, 122.90, 122.49, 120.85, 119.04, 109.40, 99.48, 79.14, 37.06, 13.70. EI-MS: $m/z = 658(\mathrm{M}^+)$.

1,3,5-Tri(6-*tert*-butyl-9-ethylcarbazol-3-yl)benzene (2k)

Yellow solid; mp 232.4–233.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 8.75$ (s, 3H), 8.30 (s, 3H), 8.04 (s, 3H), 7.93 (d, $J = 8.5$ Hz, 3H), 7.42 (m, 6H), 4.34 (d, $J = 6.8$ Hz, 6H), 1.36–1.24 (m, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 143.22$, 141.95, 139.86, 138.60, 132.39, 124.59, 122.78, 119.09, 116.69, 108.60, 108.08, 37.64, 34.68, 32.03, 13.93. EI-MS: $m/z = 826(\mathrm{M}^+)$.

1,3,5-Tri(9-ethyl-6-nitrocarbazol-3-yl)benzene (2l)

Yellow solid; mp 280.9–281.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.40$ (s, 3H), 9.10 (s, 3H), 8.39 (d, $J = 9.2$ Hz, 3H), 8.25 (d, $J = 7.2$ Hz, 6H), 7.92 (d, $J = 8.4$ Hz, 3H), 7.86 (d, $J = 9.2$ Hz, 3H), 4.62 (d, $J = 6.8$ Hz, 6H), 1.41 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 143.78$, 142.39, 141.07, 133.69, 127.40, 124.54, 123.52, 122.81, 121.94, 120.69, 118.36, 111.09, 110.04, 99.98, 38.54, 14.39. MS EI-MS: no signal. Anal. calcd. for $C_{48}H_{36}N_6O_6$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.64; H, 4.61; N, 10.72.

ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the Higher School Science and Technology Development Project of Shanxi Province Education Department (No. 2010124), the Higher School Students Science and Technology Innovation Project of Shanxi Province ([2011]11, No. 2011332), and the Project of Xinzhou Teachers University ([2011]52).

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