Synthesis of Tetrahydrothiopyrano[2,3-*b*]indole [60]Fullerene Derivatives via Hetero-Diels–Alder Reaction of C_{60} and α,β-Unsaturated Indole-2-thiones

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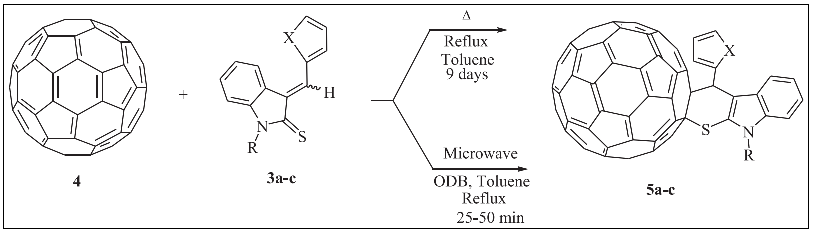

Hetero-Diels–Alder reactions of [60]fullerene with α,β-unsaturated thio-oxindoles (**3a–c**), prepared from thio-oxindole **1** and heteroaromatic aldehydes (**2a–c**), to generate tetrahydrothiopyrano[2,3-*b*]indole [60]fullerene cycloadducts (**5a–c**) under thermal or microwave irradiation were described. The yields were improved, and the reaction time was decreased by conducting the reaction under microwave irradiation.

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INTRODUCTION

The discovery of fullerenes as the first molecular allotrope of carbon [1] influenced many aspects of contemporary chemistry in the last two decades. These useful carbon-building blocks [2] with spherical symmetry, display potential applications in nanomaterial sciences [3], and medicinal chemistry [4]. In particular, the biological activity, such as a DNA cleavage [5], enzyme inhibition [6], and cytotoxicity [7] by generating singlet oxygen under visible light, gives an idea of the unabated interest in these three-dimensional molecules [8].

Besides the utility of [60]fullerene as biologically active agents, it was shown that endohedral metallofullerenes used as contrast agent in magnetic resonance imaging (MRI) [9]. For example, gadolinium endohedral metallofullerenes have been widely studied because of their magnetic contrast-enhancing properties [9,10].

On the other hand, polymer–fullerene composites, or so-called bulk heterojunctions [11] have been developed as the most effective solar cells. The high electron affinity and superior ability to transport charge make fullerenes the best acceptor component currently available for these devices [12].

Although the functionalization of [60]fullerene using organic methodologies is well established [13], studies of transition metal-catalyzed reaction of fullerene functionalization relatively poorly developed [14]. Pd-catalyzed heteroannulations of [60]fullerene with *o*-iodoanilines and anilides reported by Wang and coworkers [15]. The transition-metal catalyzed methodology for Diels–Alder cycloaddition of C_{60} has been underdeveloped. Therefore, the number of publications in metal-catalyzed [4+2] cycloaddition of [60]fullerene is limited.

Hence, the research interest on the functionalization of [60]fullerene with heterodienes has been augmented because of its unique spherical structure. One of the most powerful methods for the preparation of organofullerenes bearing a six-member heterocycle is the [4+2] cycloaddition reaction of [60]fullerene with heterodienes [16].

The synthesis of such compounds has been a focus in organic chemistry for more than two decays [17]. Two important limitations have been known for the most of the classical synthetic methods employing for these compounds. Firstly, the isolated yield for heterocycle-fused [60]fullerene derivatives are very low, and the researchers try to improve it. Secondly, the reaction time for these reactions was typically very long. It is remarkable that microwave-assisted synthesis dramatically shortened the reaction time needed compared with those by conventional heating [18] Furthermore, the yield of [60]fullerene derivatives also increased when microwave was applied [19]. For instance, the hetero-Diels–Alder reactions of [60]fullerene fused dihydropyran [20] and dihydrothiopyran [21] derivatives through C–O and C–S bond formations have been reported by Eguchi and coworkers.

Herein, we report a new synthetic route for the preparation of sulfur-bonded [60]fullerene derivatives **1** by [4+2] cycloaddition reactions.

Table 1

Organo [60]fullerene compounds **5** from α,β-unsaturated thio-oxindoles **3** and C_{60} **4**.

			Classical heating			Microwave[a]		
R	X	Product no.	*T* (°C)	Time (day)	Yield (%)	*T* (°C)	Time (min)	Yield (%)
Me	S	**5a**	Reflux	9	5	110	25	15 (35)[b]
Me	O	**5b**	Reflux	11	7	110	40	5 (20)
Me	N	**5c**	Reflux	10	6	110	40	10 (25)

[a] Power 800 W.

[b] Based on recoverd C_{60}.

RESULTS AND DISCUSSION

As a part of ongoing interest in the study and synthesis of heterocycle-fused [60]fullerene compounds [16], we were encouraged to undertake the synthesis of tetrahydrothiopyrano [2,3-*b*] indole [60]fullurene derivatives, starting with an appropriate derivatives of α,β-unsaturated thio-oxindoles (**3a–c**) and [60]fullerene. The results are summarized in Table 1. α,β-Unsaturated thio-oxindoles (**3a–c**) obtained *via* hetero-Diels–Alder reaction of thio-oxindoles **1** with heteroaromatic aldehydes (**2a–c**) (Scheme 1) [22].

As can be seen in Table 1, a wide range of α,β-unsaturated thio-oxindoles (**3a–c**) and C_{60} **4** were refluxed in toluene as solvent for 9–11 days to give the corresponding tetrahydrothiopyrano[2,3-*b*]indole [60]fullurene (**5a–c**) with low yields and high purity (Scheme 2).

To assist improving the yield of the products and decreasing the reaction time, the reaction was further investigated under microwave irradiation. A mixture of α,β-unsaturated thio-oxindoles (**3a–c**) and C_{60} **4** were reacted with molar ratio of 1:1.4 in dry Ortho Dichloro Benzene (ODCB)-toluene (1 mL). The reaction was screened under microwave irradiation for 25–50 min at 110°C, 800 W. The reaction progress was monitored by TLC in 5-min intervals. The reaction proceeded with moderate yields and high purity. The results are summarized in Table 1.

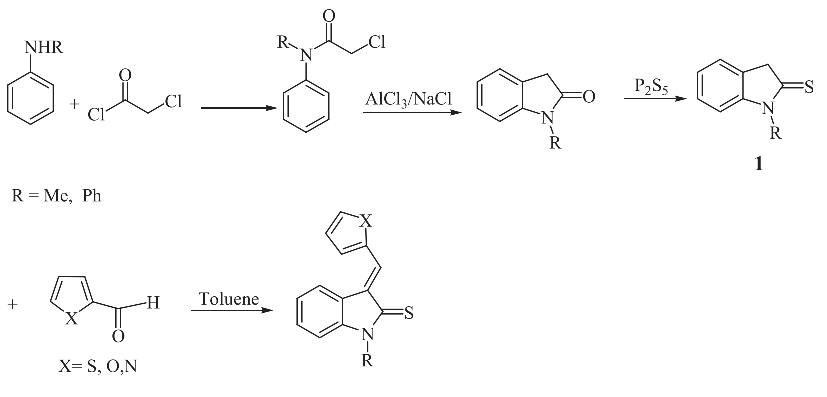
Generally, microwave-assisted reactions were carried out dielectric heating resulted from dipole–dipole interactions between polar molecules and microwave electromagnetic field. In this work, both solvent and reactants (α,β-unsaturated thio-oxindoles and [60]fullerene) are polar molecules that absorb microwave irradiation simultaneously so that the reaction proceeds via the microwave heating [23] (Scheme 3).

The structure of **5a–c** was unambiguously determined from ^{1}H NMR and ^{13}C NMR spectra in addition, UV–vis, and FTIR data. The UV–vis spectrum contained signals around at 215, 255, 316, 436 (characteristic of the 1:1 cycloadduct of [60]fullerene), and 615 nm. The weak absorption band of dihydrofullerenes around at 430 nm, confirming the presence of the [6,6] isomer.

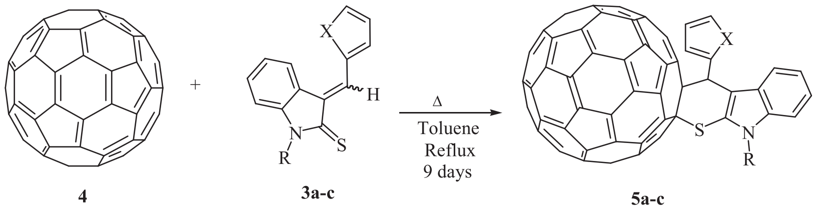
The ^{13}C NMR spectra of compound **5a** show signals due to two sp^3 junction carbons at 84 and 75 ppm. In addition to the aromatic protons, the required ^{1}H NMR signals of cycloadducts **5a–c** appeared around 6.0 ppm (CH) and 3.9 ppm (N-CH3).

A plausible mechanism for the formation of products (**5a–c**) is concerted and syn-addition, which is in accordance with the proposed mechanism for Diels–Alder reaction.

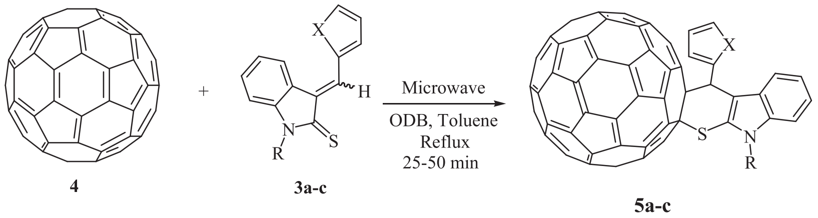
Scheme 1



Scheme 2



Scheme 3



CONCLUSION

Summarily, easily prepared α,β-unsaturated indolin-2-thiones proved to be appropriate materials for the synthesis of new macrocycle tetrahydrothiopyrano [2,3-*b*] indole [60]fullurene (**5a–c**) derivatives via [4+2] cycloaddition reaction. This reaction demonstrates that the hetero-Diels–Alder reaction of α,β-unsaturated indolin-2-thione compound is applicable to [60]fullerene, giving an irreversible cycloadduct, and a C–S bond can be formed on the [60]fullerene surface. Organofullerenes (**5a–c**) are thermodynamically stable compounds because of the aromatic character of the resulting cycloadduct, thus avoiding the undesired cycloreversion process observed in other C_{60}-based Diels–Alder reactions [24]. In particular, various substituents can be introduced on the heterocycle by employing some kinds of reagents. *o*-quinodimethanes [25], *o*-Quinone methide imines [26], and the heterocyclic analogs [27] have been successfully used to obtain stable heterocyclic organofullerenes. The driving force for this study was the novelty of the annulation of sulfur heterocycles to C_{60} core. To the best of our knowledge, this is also the first report of the synthesis of thiopyrano [2,3-*b*] indole [60]fullurene. Furthermore, under the defined reaction conditions, the cyclization process does not require the application of transition metals as catalyst or additives. High stereoselectivity, easy work-up, and single-step nature of the methodology are among the main advantages of the proposed procedure.

Having a comparison between thermal-assisted and microwave-assisted reactions, the reaction was also performed under microwave irradiation. In one representative case, the reaction under microwave irradiation was completed in 25–50 min that is much faster than the thermal reaction (9–11 days) under the same condition showing that the reaction is assisted by microwaves. Therewith, the yields of products were enhanced under microwave irradiation.

EXPERIMENTAL

All required chemicals were purchased from Merck and Fluka (Sigma-Aldrich, Darmstadt, Germany) chemical companies. All of the known compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker (Billerica, MA) DRX-300 AVANCE NMR spectrometer using $CDCl_3$ as a solvent and using tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported in parts per million (δ) downfield from TMS. All coupling constants (J) are in hertz. IR spectra were recorded on Mattson (Fremont, CA) 1000 FT-IR spectrometer using KBr pellets. Elemental analyses were run on a Perkin-Elmer (Waltham, MA) USA-2400 series. Column chromatography was performed on silica gel 40 [Merck (Kenilworth, NJ), 70–230 mesh]. TLC plate was carried out on silica gel 60 Gf-254 analytical sheets. Microwave-assisted reactions have carried out using microwave reactor [Milestone (Shelton, CT) multimode]. [60]fullerene (98%) was purchased from Bucky (Seattle, WA) company.

Synthesis of fullerene nanoparticle (4). Fullerene nanoparticle **4** were prepared in large scale by arc vaporization of graphite [28].

Preparation of α,β-unsaturated indolin-2-thiones (3a–c). To a flask containing 1 mmol of thio-oxindole **1** in toluene (5 mL), 1.2 mmol of heteroaromatic aldehydes **2a–c** was added in refluxing temperature for 4–5 h. The progress of the reaction was followed up by TLC whose spots were visualized either with UV light or with Iodine stabilized on silica gel. Reaction mixture was stirred for a given reaction time, and then, the solvent was removed under reduced pressure, and the residue was purified by column chromatography eluted with hexane-ethyl acetate.

General procedure for the synthesis of tetrahydrothiopyrano [2,3-*b*] indole [60]fullurene (5a–c) by classical heating. In a round bottom flask equipped with a stirring magnetic bar and a condenser, α,β-unsaturated indolin-2-thiones (**3a–c**) (0.079 mmol) and C_{60} **4** (40 mg, 0.055 mmol) were mixed in dry toluene (70 mL). The suspension was stirred and refluxed for 9–11 days. The reaction is monitored with TLC and UV–vis spectrum. After completion of the reaction, obtaining compounds (**5a–c**) as brown solids that finally were washed with ethyl acetate for recovering C_{60} unreacted. Afterward, the adducts were purified using column chromatography (hexane/EtOAc) from another byproducts, which identified with experimental analysis.

General procedure for the synthesis (5a-c) by microwave heating. For investigation of the reaction under microwave irradiation, a solution of C60 (40 mg, 0.055 mmol) and α,β-unsaturated indolin-2-thiones (**3a–c**) (0.079 mmol) in dry ODCB-toluene (2 mL) was irradiated at 800 W for 25–50 min. The reaction progress was monitored in 5-min intervals of irradiation using TLC. The work-up procedure used for isolation of the products was the same for that of traditional heating products. The resulting brown solution was washed with ethyl acetate, dried, and evaporated to dryness under reduced pressure. The residue was chroma-tographed on a silica gel column with hexane/ethylacetate as eluent.

Tetrahydrothiopyrano-4-thiophenyl-[2,3-b] indole [60] fullurene (5a). Brown solid (hexane/ethyl acetate); yield 15% (35% based on consumed C_{60}); IR (KBr, $\upsilon_{\max}$ cm^{1}): 2919, 2848, 1623, 1492, 1453, 1285, 1180, 526; ^{1}H NMR ($CDCl_3$): δ (ppm) 4.10 (s, 3H, NCH_3), 6.69 (s, 1H, CH tetrahydrothiopyrane ring), 7.11–7.14 (m, 4H, aromatic), 7.44–7.46 (dd, J_1 = 3.6 Hz, J_2 = 1.2 Hz, 2H, thiophen ring), 7.61–7.65 (dd, J_1 = 4.9 Hz, J_2 = 1.2 Hz, 1H, thiophen ring); ^{13}C NMR ($CDCl_3$) δ 55.4 (N-CH_3), 75.6 (CH), 77.2, 84.2 (2C sp^3); UV–vis (toluene) $\lambda_{\max}$ (nm) 254, 282, 326, 434, 706; *Anal.* Calcd for $C_{53}H_{23}NS_2$: C, 85.93; H, 2.94; N, 2.08, S, 8.70. Found: C, 86.27; H, 3.14; N, 1.90; S, 8.69.

Tetrahydrothiopyrano-4-foryl-[2,3-b] indole [60]fullurene (5b). Brown solid (hexane/ethyl acetate); 5% (17% based on consumed C60); IR (KBr, $\upsilon_{\max}$ cm^{1}): 3067, 3034, 2925, 2844, 2803, 1611, 1466, 1433, 1387, 1262, 900, 769, 747, 578; 1H NMR (CDCl3): δ (ppm) 4.02 (s, 3H, NCH3), 6.09 (s, 1H, CH tetrahydrothiopyrane ring), 7.20–7.30 (m, 4H, aromatic), 7.69–7.70 (dd, J_1 = 3.8 Hz, J_2 = 1.4 Hz, 2H, furan ring), 7.71 (dd, J_1 = 3.6 Hz, J_2 = 1.2 Hz, 1H, furan ring); 13C NMR (CDCl3): δ (ppm) 55.0 (N-CH3), 75.1 (CH), 77.2, 84.1 (2C sp^3); UV–vis (toluene) $\lambda_{\max}$ (nm): 272, 385, 432; *Anal.* Calcd for C53H23NOS: C, 88.24; H, 3.20; N, 1.95; O, 2.22; S, 4.42. Found: C, 88.19; H, 3.21; N, 1.94; O, 2.22; S, 4.44.

Tetrahydrothiopyrano-4-pyrolyl-[2,3-b]indole [60]fullurene (5c). Brown solid (hexane/ethyl acetate); 10% (25% based on consumed C60); IR (KBr, $\upsilon_{\max}$ cm^{1}): 1377, 1261, 1096, 800, 767, 526; ^{1}H NMR (CDCl3): δ (ppm) 4.10 (m, 3H, NCH3) 6.69 (s, 1H, CH tetrahydrothiopyrane ring), 7.11–7.14 (m, 4H, aromatic), 7.44–7.46 (dd, J_1 = 3.8 Hz, J_2 = 2.5 Hz, 2H, pyrrol ring), 7.61–7.65 (dd, J_1 = 2.5 Hz, J_2 = 1.4 Hz, 1H, pyrrol ring); UV–vis (toluene) $\lambda_{\max}$ (nm) 356, 436; *Anal.* Calcd for $C_{53}H_{24}N_2S$: C, 88.28; H, 3.36; N, 3.92; S, .4.42. Found: C, 88.31; H, 3.36; N, 3.89; S, 4.45.

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