The Stereoselective Synthesis of *E*-1,2-Bis(3-indolizinyl)ethylenes by the Reactions of 3-Thioformylindolizines with *n*-Tributylphosphine

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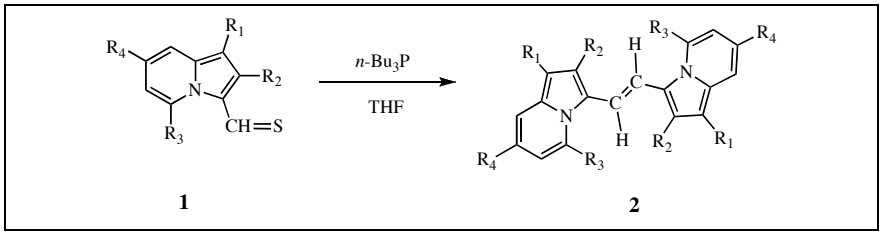

1 **2**

3-Thioformylindolizines undergo novel reductive coupling reaction in the presence of tributylphosphine to give *E*-1,2-bis(3-indolizinyl)ethylenes in high yield. These reactions proceed *via* (3-indolizinyl)methylene carbene intermediate and provide a new, stereoselective synthesis of the bis(3-indolizinyl)ethylene derivatives highly.

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INTRODUCTION

Stilbene derivatives have a wide range of biological activity [1]. Their unique photoelectronic properties have also drawn much recent research interest [2]. Replacing the two phenyls in stilbenes by heterocycles leads to their heterocyclic analogs. In comparison with stilbenes, these heterostilbenes have many different and special properties. As examples, many heterostilbenes have significantly red shifted absorption and emission spectra [3], increased molecular polarizability [4], more sensitive response to external electric and magnetic field change [5], *etc*. As a result, heterostilbenes have gained wide applications in diversified areas such as nonlinear optics [6], solvatochromism [7], *etc*. In response to the increasing applications of heterostilbenes, their synthesis has emerged as an active new research area [8].

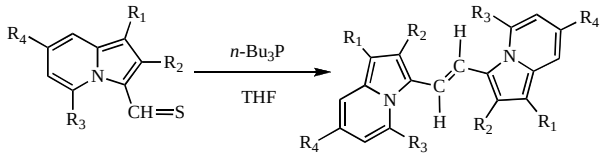
The chemical reactions of thiocarbonyl compounds have been of much research interest because of their application in the synthesis of heterocycles and natural products, and in C-C bond formation [9]. It is anticipated that the smaller steric hindrance at the thiocarbonyl group in thioaldehyle as compared to the thioketones would enable the former to undergo more diversified reactions. However, thioaldehydes are usually unstable and are prone to oligomerize [10], and only when either electronic stabilization or steric protection to the thioformyl functionality exists can thioaldehydes be stable at ambient temperature. Therefore, the chemistry of thiocarbonyl compounds have been mainly investigated with thioketones as substrates [9,10], while the thioaldehyde chemistry is much less explored. Belonging to the small group of known stable thioaldehydes, 3-thioformylindolizines [11] have their stability inherently originating from the extensive electron delocalization between the thioformyl and the strongly electron donating and π- electron excessive indolizinyl. Indolizine derivatives themselves constitute an important and interesting class of heterocycles with special electronic structure and increasing applications in medicinal chemistry [12] and in optical and electronic materials [13]. Therefore, their synthesis and structural elaboration have also received much recent attention [14]. Since 3-thioformylindolizines are relatively easily accessible [11], we envision that not only they may serve as good model compounds to investigate the reactivity of thioaldehydes, but also the reactions of thioformylindolizines may provide new synthetic methods for the structural modification of indolizines. We repot here the reductive coupling reactions of 3-thioformylindolizines in the presence of *n*-tributylphosphine, leading to the highly stereoselective synthesis of the novel stilbene heterocyclic analogue *E*-1,2-bis(3-indolizinyl)ethylenes in good yield.

RESULTS AND DISCUSSION

Reactions of 3-thioformylindolizines **1a**-**1g** with two phosplines (triphenylphosphine, *n*-tributylphosphine) were tested. It is found that, refluxing **1a** with 3~4 equivalent amount of triphenylphosphine in dry THF under nitrogen atmosphere for 16 h resulted in no appreciable reaction as evidenced by TLC monitoring of the reaction course. However, refluxing **1a** with the more nucleophilic *n*-tributylphosphine under similar conditions led to smooth reaction, which was completed within 10 h. Chromatographic separation of the reaction mixture afforded an orange colored product which, according to spectroscopic (^{1}H NMR, IR, MS) and elemental analytical data, turned out to be the *E*-1,2-bis(2-phenyl-3-indolizinyl)ethylene **2a** (Scheme 1 and Table 1). Different conditions for this reaction were examined. Reaction of **1a** with *n*-Bu_3P in refluxing DMF resulted in lower yield caused by the

occurrence of side reactions. Reaction in THF at lower temperature, on the other hand, led to a lengthening of reaction time. Increasing the amount of *n*-Bu_3P shortened the reaction time, however, the separation process was found to be hampered by the necessity of removing of the excess amount of *n*-Bu_3P after the reaction. The optimal results were found to be achieved by refluxing the thioformylindolizine with the *n*-Bu_3P in a 1:3.5 mole ratio in THF under nitrogen atmosphere until the disappearance of the thioformylindolizine as indicated by TLC monitoring. Under these conditions, reactions of **1b**-**1g** were similarly conducted to give the corresponding *E*-1,2-biindolizin-3-yl ethylenes **2b**-**2g** [15]. The results are in Table 1.

Scheme 1



1 **2**

Table 1

Reactions of 3-thioformylindolizenes (**1**) with *n*-tributylphossphine.

Entry	R_1	R_2	R_3	R_4	Time / h	Yield/%
2a	H	Ph	H	H	10	84
2b	CH_3	Ph	H	H	8	84
2c	H	Ph	H	CH_3	10	86
2d	CH_3	CH_3	H	H	14	79
2e	H	*t*-Bu	H	H	34	90
2f	CH_3	*t*-Bu	H	H	18	93
2g	H	CH_3	H	CH_3	12	91

An X-ray crystallographic analysis of **2d** was carried out, and the ORTEP drawing and cell packing diagram are given in Figure 1 and 2 respectively. Figure 1 clearly shows the *E*-configuration of **2d**. It is also seen that, in **2d**, the two indolizines are coplanar with the central C=C bond, constructing a large delocalized π-system. This enables favorable intermolecular interactions in the crystal packing and resulted in π-π-stacking as indicated by the interlayer distance of 3.7 Å [16]. The *E*-configuration of the other *E*-1,2-biindolizin-3-ylethylenes can be deduced from the chemical shift of the olefinic protons in the ^{1}H NMR spectra.

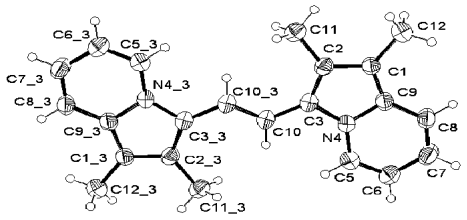


Figure 1. Molecular structure of **2d**.

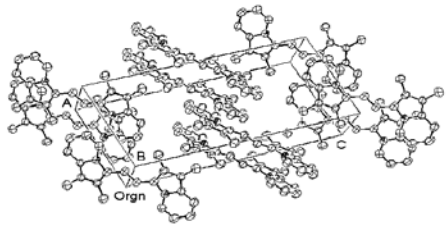


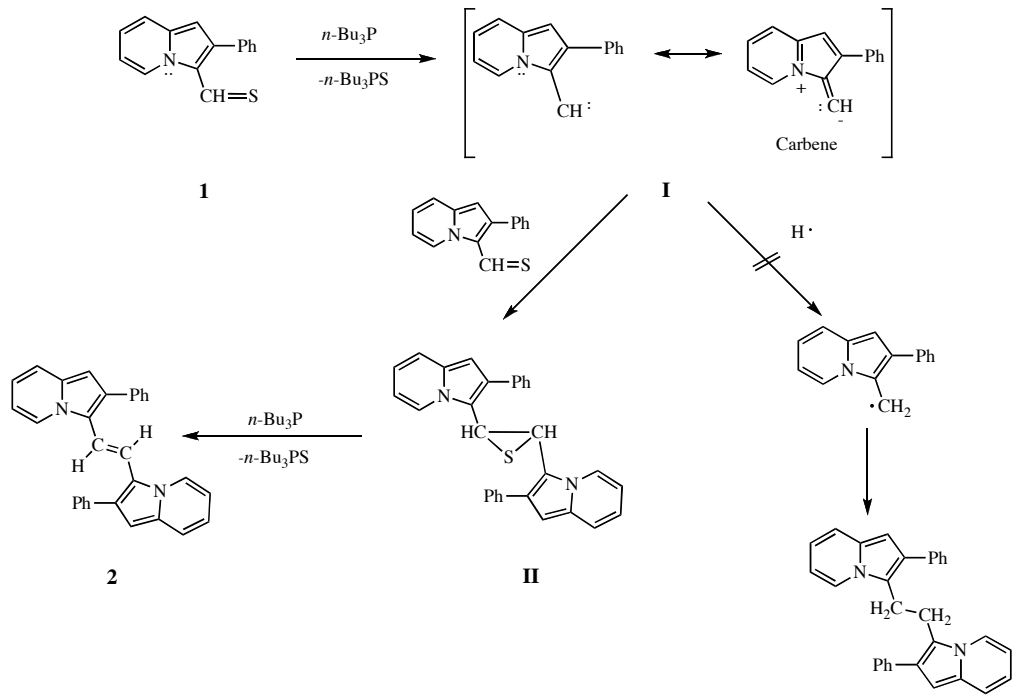
Figure 2. Packing diagram of **2d**.

These reactions displayed significant difference with the reactions of thioketones with phosphines. Ogata *et al*. reported that in the reaction of thiobenzophenone with tributylphosphine [17], 1,1,2,2-tetraphenyl ethane was the main product (65 %), and the olefinic product (tetraphenyl ethene) was a minor product (28 %), in the reaction of thio-fluorenone with tributylphosphine [18], bifluorenylidene (63 %) was the main product, and bifluorenyl was a minor product.

In our reaction of the thioaldehydes **1** with the phosphine, however, we have not found any hydrogenated product of **2**. A plausible mechanism for this reaction is proposed in Scheme 2. Similar to that in the reactions of thioketones with phosphine [18], desulfurization by the trivalent phospine Bu_3P leads to a (3-indolizinyl)methylene intermediate **I**.

Addition of this carbene to the C=S bond of another 3-thioformylindolizine gave the thiirane **II**. Thiiranes are known to undergo facile desulfurization in the presence of phosphines [18]. Desulfurization of **II** either spontaneously under thermal conditions or promoted by the phosphine resulted in the formation of the ethylene products **2**. The ground state of arylcarbenes is proposed to be the triplet state [19]. In the reactions of thioketone with phosphines [18], hydrogen abstraction of the triplet carbene [diphenylmethylene and (9-fluorenyl)methylene] from tributylphosphine and addition to the C=S bond of the second thioketone run parallelly, with the hydrogen abstraction being predominant, giving the ethanes as main products and the ethylene as minor products. In the case of the reactions of **1** with *n*-Bu_3P, much smaller steric hindrance toward the carbene addition to the thioformyl as compared with the addition to the more sterically hindered thiocarbonyl in thioketones may contribute to the prevailing addition to C=S bond at the expense of hydrogen abstraction. Moreover, the hydrogen abstraction reactivity of the indolizinylcarbene may be further decreased by the effective mesomeric stabilization as shown in **I** (Scheme 2). In the triplet diradical intermediate formed during the addition of the triplet carbine to the C=S bond, serious steric hindrance between the two indolizinyls in the *cis*- conformation renders the *trans*-conformation to be predominant, which after

Scheme 2



intersystem crossing and bond formation affords the thiirane with *trans*-configuration.

In summary, 3-thioformylindolizines undergo novel desulfurazative coupling reactions in the presence of *n*-tributylphosphine to give *E*-1,2-bis(3-indilizinynyl) ethylenes stereoselectively in satisfactory yield. These reactions provided a new efficient and stereospecific synthesis of *E*-1,2-bis(3-indilizinynyl)ethylenes, and displayed the different reaction pattern of these indolizine thioaldehydes in reactions with phosphine from the reaction of thioketones with phosphines.

EXPERIMENTAL

Melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR Spectra were recorded on a Nicolet FT-IR 5DX spectrometer with KBr pellets. ^{1}H NMR Spectra were recorded on a Bruker ACF-300 spectrometer with TMS as internal reference. Mass spectra were obtained on a ZAB-HS mass spectrometer at 70 eV. Elemental analytical were performed on a Foss Heraeus CHN-O-Rapid analyzer.

General procedure for preparation of (*E*)-1,2-bis(3-indolizinyl)ethene (2a-g).A solution of 2-phenyl-3-thioformyl-indolizine (**1a**) (0.35 g, 1.5 mmol) in anhydrous THF (8 mL) was stirred at r.t. and after the air was replace by N_2 gas, adding tributylphosphine (1.1 g, 5.4 mmol). The reaction was kept at reflux temperature till **1a** disappeared (monitored by TLC). The solvent was removed *in vacuo*, the mixture was cooled and the *E*-1,2-bis(2- phenyl-3-indolizinyl)ethylene (**2a**) was separated on a column of silica gel G with petroleum ether as eluents for quick elution. Under these conditions, reaction of **1b**-**1g** were similarly conducted to give the corresponding *E* -1,2-bis(3-indolizinyl)-ethylenes **2b-2g.**

***(E)*-1,2-Bis(2-phenylindolizin-3-yl)ethene (2a).** Orange crystals; m.p. 198-200 °C (from acetone). ir (KBr): ν_{max} 3054, 3025, 1625, 1597, 962, 760, 725, 700 cm^{-1}. ^{1}H nmr (300MHz, DMSO-d_6): δ = 8.42 (d, 2H, J = 7.0 Hz, H-5, H-5'), 7.49 (d, 2H, J = 8.7 Hz, H-8, H-8'), 7.36-7.29 (m, 10H, 2×Ph), 7.03 (s, 2H, *trans*, -CH =CH-), 6.82 (m, 2H, H-7, H-7'), 6.70 (m, 2H, H-6, H-6'), 6.58 (s, 2H, H-1, H-1'). MS *m/z* (%): 410 (M$^+$, 84), 230 (100), 205 (17), 193 (5). *Anal.* Calcd. for $C_{30}H_{22}N_2$ (%): C, 87.80; H, 5.37; N, 6.83. Found (%): C, 87.75; H, 5.44; N, 6.89.

***(E)*-1,2-Bis(1-methyl-2-phenylindolizin-3-yl)ethene (2b).** Orange crystals; m.p. 226-228 °C (from petroleum ether). ir (KBr): ν_{max} 3066, 3023, 2916, 1753, 1600, 951, 733, 700 cm^{-1}. ^{1}H nmr (300 MHz, C_6D_6): δ = 7.56-7.53 (m, 6H, H-5, H-5', 2×Ph), 7.41-7.31 (m, 6H, 2×Ph), 7.23 (d, 2H, J = 8.9 Hz, H-8, H-8'), 6.87 (s, 2H, *trans*, -CH=CH-), 6.50 (m, 2H, H-7, H-7'), 6.28 (m, 2H, H-6, H-6'), 2.29(s, 6H, 2×CH_3). MS *m/z* (%): 438 (M$^+$, 100), 244 (68); *Anal.* Calcd. for $C_{32}H_{26}N_2$ (%): C, 87.67; H, 5.94; N, 6.39. Found (%): C, 87.53; H, 6.08; N, 6.42.

***(E)*-1,2-Bis(7-methyl-2-phenylindolizin-3-yl) ethene (2c).** Orange crystals; m.p. 240-242 °C (from petroleum ether). ir (KBr): ν_{max} 3046, 3020, 2904, 1638, 1598, 961, 754, 711 cm^{-1}. ^{1}H nmr (300MHz, C_6D_6): δ = 7.68(d, 4H, J = 1.47Hz, 2×Ph), 7.65 (d, 2H, J = 1.15 Hz, H-5, H-5'), 7.25 (m, 6H, 2×Ph), 7.01 (s, 2H, H-8, H-8'), 6.84 (s, 2H, *trans*,-CH=CH-), 6.50 (s, 2H, H-1, H-1'), 5.96 (m, 2H, H-6, H-6'), 1.9 (s, 6H, 2×CH_3). MS *m/z* (%): 438 (M$^+$, 79), 244 (50), 219 (24), 207 (100); *Anal*. Calcd. for $C_{32}H_{26}N_2$ (%): C, 87.67; H, 5.94; N, 6.39. Found (%): C, 87.62; H, 6.02; N, 6.34.

***(E)*-1,2-Bis(1,2-dimethylindolizin-3-yl)ethene (2d).** Yellow crystals; m.p. 180-182 °C (from petroleum ether). ir (KBr): ν_{max} 3058, 3032, 2961, 2907, 1755, 1674, 933, 721 cm^{-1}. ^{1}H nmr (300

MHz, C_6D_6): δ = 7.83 (s, 2H, H-5, H-5'), 7.29 (s, 2H, H-8, H-8'), 7.03 (s, 2H, *trans*, -CH=CH-), 6.55 (s, 2H, H-7, H-7'), 6.29 (m, 2H, H-6, H-6'), 2.47 (s, 6H, 2×CH_3), 2.34 (s, 6H, 2×CH_3). MS *m/z* (%): 314 (M^+, 100), 299 (50), 182 (53), 157 (15); *Anal.* Calcd. for $C_{22}H_{22}N_2$ (%): C, 84.00; H, 7.01; N, 8.92. Found (%):C, 84.01; H, 7.08; N, 9.06.

***(E)*-1,2-Bis(2-*t*-butylindolizin-3-yl)ethene (2e).** Yellow crystals; m.p. 160-162 °C (from petroleum ether). ir (KBr): ν_{max} 3116, 3038, 2961, 2862, 976, 737 cm^{-1}. ^1H nmr (300 MHz, DMSO-d_6): δ = 8.54 (d, 2H, J = 7.0 Hz, H-5, H-5'), 7.44 (d, 2H, J = 8.8 Hz, H-8, H-8'), 7.13 (s, 2H, *trans*, -CH=CH-), 6.73 (m, 2H, H-7, H-7'), 6.62 (m, 2H, H-6, H-6'), 6.46 (s, 2H, H-1, H-1'), 1.38 (s, 18H, 2×*t*-Bu). MS *m/z* (%): 370 (M^+, 100), 313 (53), 210 (72), 185 (19); *Anal.* Calcd. for $C_{26}H_{30}N_2$ (%): C, 84.32; H, 8.11; N, 7.57. Found (%): C, 84.24; H, 8.07; N, 7.42.

***(E)*-1,2-Bis(1-methyl-l,2-*t*-butylindolizin-3-yl)ethene (2f).** Yellow crystals; m.p. 186-188 °C (from acetone). ir (KBr): ν_{max} 3067, 3030, 2956, 2865, 1616, 981, 735 cm^{-1}. ^1H nmr (300MHz, Acetone-d_6): δ = 8.54 (d, 2H, J = 6.0 Hz, H-5, H-5'), 7.39 (d, 2H, J = 9.0 Hz, H-8, H-8'), 7.06 (s, 2H, *trans*, -CH=CH-), 6.64 (m, 2H, H-7, H-7'), 6.49 (m, 2H, H-6, H-6'), 2.46 (s, 6H, 2×CH_3-), 1.47 (s, 18H, 2×*t*-Bu). MS *m/z* (%): 398 (M^+, 75), 341 (100), 224 (25), 199 (20); *Anal.* Calcd. for $C_{28}H_{34}N_2$ (%): C, 84.42; H, 8.54; N, 7.04. Found (%): C, 84.57; H, 8.70; N,6.85.

***(E)*-1,2-Bis(2,7-dimethylindolizin-3-yl)ethene (2g).** Orange crystals; m.p. 199-201 °C (from petroleum ether). ir (KBr): ν_{max} 3098, 3046, 2954, 2907, 1638, 940, 753 cm^{-1}. ^1H nmr (300 MHz, C_6D_6): δ = 7.79 (s, 2H, H-5, H-5'), 7.03 (s, 4H, H-8, H-8', *trans*,-CH=CH-), 6.48 (s, 2H, H-1, H-1'), 6.16 (d, 2H, J = 6.9 Hz, H-6, H-6'), 2.60 (s, 6H, 2×CH_3), 2.13 (s, 6H, 2×CH_3). MS *m/z* (%): 314 (M^+, 100), 299 (38), 182 (77), 157 (26); *Anal.* Calcd. for $C_{22}H_{22}N_2$ (%): C, 84.00; H, 7.01; N, 8.92. Found (%): C, 84.06; H, 7.00; N, 8.85.

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