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# One pot synthesis of fused [1,2-*a*]pyrrole from 1,6-dioxo-2,4-diene and haloalkyl primary amine

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**Abstract**—The one pot synthesis of fused 2,3-dihydropyrrolizine **4a** and 6,7-dihydro-5*H*-indolizine **4b** involving the intermolecular dehydrative condensation of 1-phenyl-1,6-dioxo-hepta-2,4-diene **1** with 2-chloroethylamine and 3-chloropropylamine followed by the intramolecular cyclization of the intermediary products 2-(1-chloroalkyl-5-methylpyrrol-2-yl)-1-phenylethanones **3a**,**b** in the presence of a base such as $Na_2CO_3$ and $NaHCO_3$ is described. These also led to the concurrent formation of the oxidatively dimerized product 2,3-bis-[1,5-(2-chloroalkyl)-1-*H*-pyrrol-2-yl]-1,4-diphenylbutane-1,4-dione **5a**,**b** whereby the structure was further confirmed by X-ray analysis.


## 1. Introduction

The fused [1,2-*a*]pyrroles are important scaffold of alkaloids widely isolated from plants, insects, animals, oceanic lives and secondary metabolites of microbes and have potent biological activities.[1–3] The synthesis of pyrrolizines and indolizines continues to attract the attention of organic chemist and numerous synthetic routes have been reported.[4–14] Our previous study demonstrated 1,6-dioxo-2,4-diene to a versatile intermediate in the synthesis of pyrrole derivatives.[15] The important feature of the pyrrole derivates formed is that the hydrogen atom at the carbon atom attached to the 2-position can be readily deprotonated for reaction with an electrophilic center at the *N*-tether to give fused [1,2-*a*]pyrroles. Based on this methodology, we have recently developed a new pathway for the synthesis of pyrrolizines and indolizines.[16] The moderate yield of the pyrrolizine and indolizine derivatives with this approach may be attributed to the reversible condensation reaction (Dieckmann/Thrope) used for the intramolecular ring closure reaction. We felt that greater potential utility for the construction of fused [1,2-*a*]pyrroles could be realized were we to achieve intramolecular cyclization by an irreversible alkylation reaction. Herein, we report our further investigations on the use of an irreversible alkylation reaction for the intramolecular ring closure reaction with the hope of improving the yield. To affect an intramolecular alkylative cyclization, we required the construction of *N*-tether haloalkylpyrrole derivatives. Furthermore the appropriate choice of base might led to the development of a one-pot procedure to prepare pyrrolizine and indolizine derivatives from the reaction of 1-phenyl-1,6-dioxo-hepta-2,4-diene **1** with chloroethylamine and chloropropylamine, respectively (Scheme 1).

## 2. Results and discussion

Our starting point was the 1-phenyl-1,6-dioxo-hepta-2,4-diene, **1**, which we have previously prepared from the reaction of 2-methylfuran with α-diazoacetophenone according to the method of Wenkert.[17] It has been demonstrated earlier that compound **1** reacted with alkylamines to give *N*-tether alkylpyrrole derivatives. Originally, it was thought that the preparation of *N*-tether haloalkylpyrroles from **1** and aminoalkyl halide under the same condition would be met with competing reaction arising from the self-condensation of the aminoalkyl halide. Therefore, our initial strategy for the synthesis of *N*-tether haloalkylpyrrole involved the reaction of **1** with amino alcohol to form *N*-tether hydroxyalkylpyrrole, followed by a subsequent conversion of the alcohol to the corresponding halide. Compound **1** react with 1-aminoethanol and 1-aminopropanol to give *N*-tether hydroxyalkylpyrrole derivatives **2a** and **2b**, respectively, but in a moderate yield (40–50%). The alcohol functionality in **2a** and **2b** can be converted to the chloride **3a** and **3b** in a near quantitative yield. The overall yields from the two steps were only

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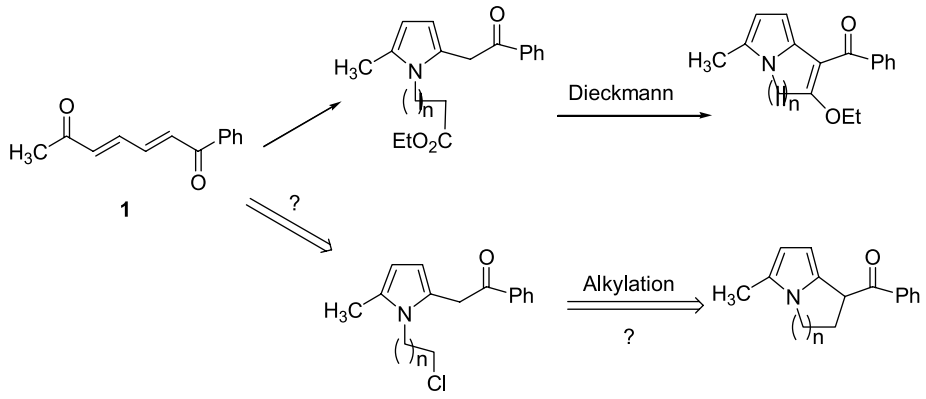
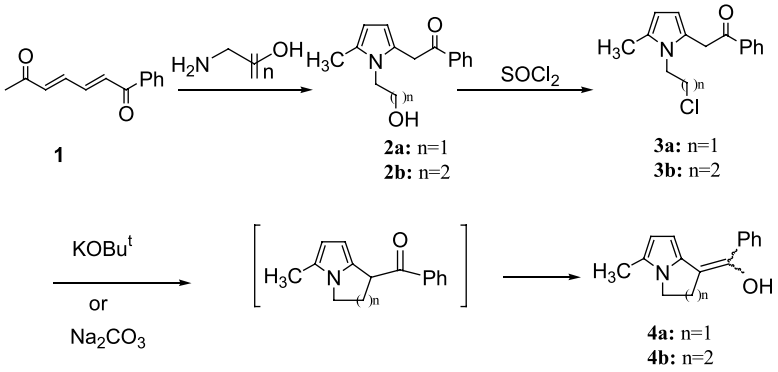



**Scheme 1.** Synthetic approach towards pyrrolizine and indolizine.

moderate. Next, the intramolecular cyclization of **3a** and **3b** was attempted using potassium *t*-butoxide.[16] Although, submission of **3a** and **3b** under this intramolecular alkylative cyclization condition gave the pyrrolidine **4a** and indolizine **4b** respectively, the yield was rather low (20–25%) (Scheme 2). The $^{1}H$ and $^{13}C$ NMR spectra of **4a** and **4b** revealed the absence of an α-methine hydrogen between the pyrrole and the carbonyl group, and this was attributed to the formation of the more stable enol-form due to resonance delocalization. The ketone–enol tautomerizaton of indolizone derivatives has been reported.[9]

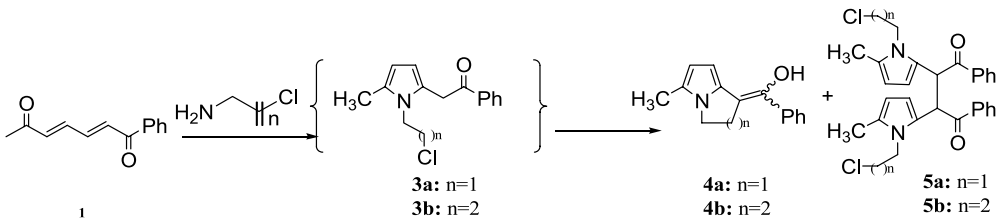
Although the synthesis of pyrrolidine and indolizine were realized, the poor overall yield hampered its practicality. A trial experiment for the reaction of **1** with chloroethylamine was carried out and fortuitously gave **3a** in a ca. 90–95% yield. Similarly, reaction of **1** with chloropropylamine gave **3b** in similar yield. Clearly, the chloroalkylamine did not proceed to give self-polyalkylation products. A greater challenge was to improve the yield during the intramolecular alkylative cyclization step. Several different bases can be called into play and we choose to use sodium carbonate in methanol for its mild condition. Reaction of **3a** and **3b** with sodium carbonate in methanol successfully gave **4a** and **4b** in a dramatically improved yield (55–65%), together with an isolable minor product (5–10%) in each case that was not identified at this stage.

An important requirement for the successful one pot reaction is the non-participation of the base prior to alkylation reaction, allowing the smooth formation of pyrrole intermediate from the reaction of **1** with aminoalkyl halide. The discovery of the sodium carbonate promoted cyclization reaction above point the way for a facile design of a fast one-pot synthesis of fused [1,2-*a*]pyrroles. It was reasoned that sodium carbonate in methanol would not exacerbate the problem of self-condensation of the aminoalkyl halide during its reaction with **1** to form the pyrrole intermediate at the onset of the reaction. In a typical experiment, **1** was reacted with chloroethylamine in the presence of sodium carbonate and the reaction mixture stirred under a nitrogen atmosphere at room temperature in methanol. TLC was used to monitor the progress of the reaction. The TLC showed a complete disappearance of the starting material **1** after 2 h at room temperature, the major product was found to be the pyrrole derivative **3a**. Next, the reaction was carried out for a longer reaction time (72 h) until TLC indicated the total consumption of **1** and the disappearance of intermediate **3a**. This resulted in the formation of two new products **4a** and **5a** in a 3:1 ratio. The major product was the required pyrrolizine derivative **4a**. The minor product **5a** showed a parent peak in the mass spectrum at *m*/*z* 520, 522, 524 (approx. 10:6:1 ratio), an equivalent to 2 units less than that for two molecules of **3a** and a pattern indicating the presence of two chlorine atoms. From this data we tentatively assigned **5a** as 2,3-bis(1*H*-pyrol-2yl)-1,4-diphenyl-1,4-dione, the oxidatively dimerized product of the intermediate **3a**. Oxidative coupling of enolates, especially phenylacetic acid ester, through a variety of methods have been widely reported.[18] At this




**Scheme 2.**

**Table 1**. Product distribution for the reaction of **1** with aminoalkyl halide and $Na_2CO_3$/$NaHCO_3$




| Entry | Reaction time (h) | $Na_2CO_3$/MeOH (ratio) | Entry | Reaction time (h) | $NaHCO_3$/MeOH (ratio) |
|---|---|---|---|---|---|
| 1 | 2 | **3a** only 85–90% | 5 | 2 | **3a** only 85–90% |
| 2 | 72 | **4a/5a** (3:1) 65% | 6 | 72 | **4a/5a** (1:4) 77% |
| 3 | 2 | **3b** only 85–90% | 7 | 2 | **3b** only 85–90% |
| 4 | 72 | **4b/5b** (3:1) 70% | 8 | 72 | **4b/5b** (1:4) 80% |

point, we were uncertain of the stereoisomers of the dimer, *dl*- or *meso*-**5a**. The formation of products **4a** and **5** reflect two competing reactions pathway for the intermediate **3a**, one leading to an intramolecular alkylation and the other oxidative coupling.

This one pot strategy can be applied to the synthesis of indolizine derivative **4b** by treatment of 1-phenyl-1,6-dioxo-hepta-2,4-diene **1** with 3-chloropropylamine and sodium carbonate in methanol for 72 h. In this case we also obtained two products, the indolizine derivative **4b** and **5b** in a 3:1 ratio (70% overall yield). The results are summarized in Table 1. A one pot synthesis of indolizines from the reaction of acyl bromide, pyridine and acetylene mediated by microwave has been reported.[19] The mass spectrum of **5b** again correlates to 2 units less than for two molecules of **3b**. We were able to obtain a crystal of **5b** suitable for X-ray crystallographic analysis[20] (Fig. 1) and this unambiguously supported the oxidative coupling product of the intermediate **3b**. The oxidative coupling reaction proceeds to give the *dl* **5b** stereoisomer. Similar high selectivity of *dl* isomer over *meso* isomer has also been reported for the oxidative coupling of phenylacetic acid ester by treating the ester with titanium chloride and then adding triethylamine to the resulting solution.[18h]

Since pyrrolidine **4a** and indolizine **4b** were form in good yield using sodium carbonate in methanol, we assumed that the use of an even milder base such as sodium bicarbonate for the one pot synthesis might further improved the yield. Contrary to expectation, the reaction of **1** with 2-chloroethylamine with sodium bicarbonate in methanol for 72 h was found to give a reverse preponderance of products **4a** and **5a** in a 1:4 ratio (77% overall yield). Similarly, the reaction of **1** with chloropropylamine gave **4b** and **5b** in a ratio of 1:4. The formation of the dimer in these reactions might be explained in consideration of the redox reaction occurring between the generated carbanion of the intermediate **3** and the free **3** or the product **5** which play the role as a single electron acceptor, leading to the formation of the benzoylmethyl radical and the anion radical of **3** or **5**. Accordingly, in the one pot reaction, the use of sodium bicarbonate will give a greater preponderance of the dimeric product **5**.

## 3. Conclusion

In summary, this paper presents a simple and convenient one pot synthesis of pyrrolizine and indolizine skeletons from the reaction of 1,6-dioxo-2,4-diene and chloroalkylamine in methanol with sodium carbonate in high yield, and under mild condition. Furthermore, the results in this paper clearly show that the use of sodium bicarbonate gave mainly the oxidative coupling product and this has not been reported.

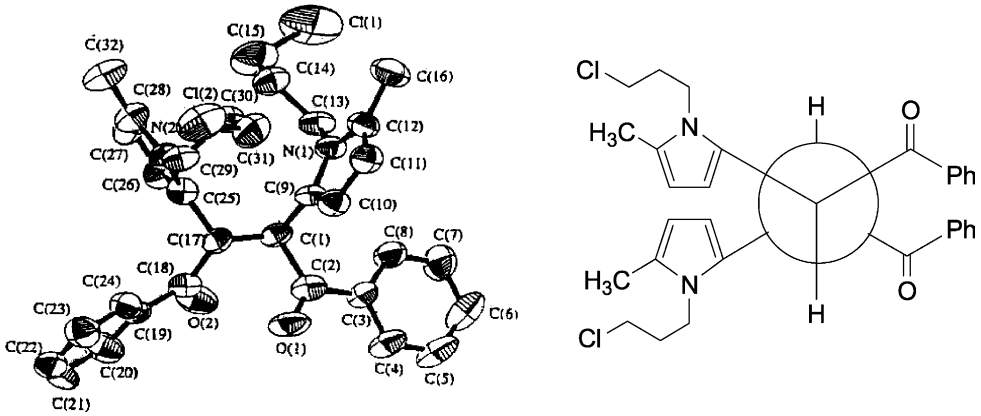



**Figure 1.** X-ray structure of compound **5b** showing the most stable Newman conformation.

## 4. Experimental

### 4.1. General experimental conditions

Compound **1** was prepared according to previously reported method.[16] Commercially available reagents were used without further purification. $^{1}H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard.

### 4.2. General procedure of pyrrole ring formation 2 and 3 from the reaction of 1 with aminoalkyl alcohol and chloroalkylamine

To a stirred solution of aminoalkyl alcohol (1.30 mmol) in MeOH (20 mL) at 0 °C was added **1**. The reaction was stirred at 0 °C for 2 h and left at room temperature overnight. The MeOH was removed under reduce pressure and the crude product extracted by $CH_2Cl_2$. The crude product obtain was purified by preparative TLC to provide the corresponding product.

The chloroethyl- or chloropropylamine hydrochloride salt (1.10 mmol) was used and have to be neutralized with an equivalent of $Na_2CO_3$.

**4.2.1. [*N*-(2-Hydroxyethyl)-5-methylpyrrol-1-yl]phenylethanone (2a).** Obtained as yellow oil in 45% yield (EtOAc/hexane, 1:5). $\nu_{max}$: 3416, 1685 $cm^{-1}$. $^{1}H$ NMR (200 MHz): $\delta$ 8.03 (m, 2H), 7.56 (m, 3H), 5.96 (d, $J$=3.6 Hz, 1H), 5.86 (d, $J$=3.6 Hz, 1H), 4.25 (s, 2H), 3.98 (t, $J$=7.2 Hz, 2H), 3.78 (t, $J$=7.2 Hz, 2H), 2.24 (s, 3H), 1.61 (brd, 1H); MS (EI) *m/z* 243(37). HRMS *m/z* calcd for $C_{15}H_{17}NO_2$, 243.1259; found, 243.1257.

**4.2.2. [*N*-(2-Hydroxypropyl)-5-methylpyrrol-1-yl]phenylethanone (2b).** Obtained as yellow oil in 40% yield (EtOAc/hexane, 1:5). $\nu_{max}$: 3400, 1681 $cm^{-1}$. $^{1}H$ NMR (200 MHz): $\delta$ 8.04 (m, 2H), 7.58 (m, 3H), 5.93 (d, $J$=3.6 Hz, 1H), 5.82 (d, $J$=3.6 Hz, 1H), 4.26 (s, 2H), 3.81 (t, $J$=7.1 Hz, 2H), 3.68 (t, $J$=7.1 Hz, 2H), 2.22 (s, 3H), 2.04 (brd, 1H), 1.68 (m, 2H); MS (EI) *m/z* 257(26). HRMS *m/z* calcd for $C_{16}H_{19}NO_2$, 257.1416; found, 257.1415.

**4.2.3. [*N*-(2-Chloroethyl)-5-methylpyrrol-1-yl]phenylethanone (3a).** Obtained as yellow oil in 90% yield (EtOAc/hexane, 1:5). $\nu_{max}$: 1685 $cm^{-1}$. $^{1}H$ NMR (200 MHz): $\delta$ 8.06 (m, 2H), 7.58 (m, 3H), 5.91 (d, $J$=3.4 Hz, 1H), 5.88 (d, $J$=3.4 Hz, 1H), 4.29 (s, 2H), 4.12 (t, $J$=7.3 Hz, 2H), 3.63 (t, $J$=7.3 Hz, 2H), 2.25 (s, 3H); MS (EI) *m/z* 261(12), 263(36). Anal. Calcd for $C_{15}H_{16}ClNO$: C, 68.83; H, 6.16; N, 5.38. Found C, 68.55; H, 6.15; N, 5.26.

**4.2.4. [*N*-(2-Chloropropyl)-5-methylpyrrol-1-yl]phenylethanone (3b).** Obtained as yellow solid in 95% yield (EtOAc/hexane, 1:5), mp 75–58 °C. $\nu_{max}$: 1685 $cm^{-1}$. $^{1}H$ NMR (200 MHz): $\delta$ 8.05 (m, 2H), 7.54 (m, 3H), 5.91 (d, $J$=3.6 Hz, 1H), 5.89 (d, $J$=3.6 Hz, 1H), 4.28 (s, 2H), 3.97 (t, $J$=7.0 Hz, 2H), 3.54 (t, $J$=7.0 Hz, 2H), 2.25 (s, 3H), 2.08 (m, 2H); MS (EI) *m/z* 275(13), 277(39). Anal. Calcd for $C_{16}H_{18}ClNO$: C, 69.68; H, 6.58; N, 5.08. Found C, 69.65; H, 6.55; N, 5.11.

### 4.3. KOBu$^t$ as base for alkylative cyclization

To a solution of KOBu$^t$ (0.65 mmol) in anhydrous THF (20 mL) under $N_2$ at 0 °C was added **3a/b** (0.65 mmol). The reaction was allowed to warm to ambient temperature and stirred for 6 h. The reaction was quenched with water and the THF removed under reduced pressure, and then extracted with $CH_2Cl_2$. The crude product obtained was purified by preparative TLC to give **4a/b**, respectively.

**4.3.1. 1-((*E*)-1-Hydroxybenz-1-ylidene)-5-methyl-2,3-dihydro-1*H*-pyrrolizine (4a).** Obtained as yellow oil in 20% yield (ether/hexane, 1:3). $\nu_{max}$: 3400, 1615 $cm^{-1}$. $^{1}H$ NMR (200 MHz): $\delta$ 7.98 (d, 2H), 7.60 (m, 1H), 7.52 (m, 2H), 6.89 (d, $J$=3.9 Hz, 1H), 6.05 (d, $J$=3.9 Hz, 1H), 4.69 (t, $J$=6.0 Hz, 2H), 3.95 (t, $J$=6.0 Hz, 2H), 2.41 (s, 3H); $^{13}C$ NMR (50 MHz) $\delta$ 193.35, 183.21, 142.17, 134.21, 133.53, 130.00, 128.82, 128.75, 126.94, 125.66, 110.87, 43.38, 42.12, 33.61, 12.50; MS (EI) *m/z* 225(16). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found C, 79.78; H, 6.67; N, 6.17.

**4.3.2. 8-((*E*)-1-Hydroxybenz-1-ylidene)-3-methyl-5,6-dihydro-8*H*-indolizine (4b).** Obtained as yellow oil in 25% yield (ether/hexane, 1:3). $\nu_{max}$: 3400, 1615 $cm^{-1}$. $^{1}H$ NMR (200 MHz): $\delta$ 8.00 (d, 2H), 7.64 (m, 1H), 6.85 (d, $J$=4.0 Hz, 1H), 6.03 (d, $J$=4.0 Hz, 1H), 4.56 (t, $J$=5.8 Hz, 2H), 3.64 (t, $J$=5.8 Hz, 2H), 2.38 (s, 3H), 2.30 (m, 2H); $^{13}C$ NMR (50 MHz) $\delta$ 193.35, 182.21, 142.17, 134.21, 133.53, 130.00, 128.82, 128.75, 126.94, 125.66, 110.87, 43.38, 42.12, 33.61, 12.50; MS (EI) *m/z* 239(25). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found C, 80.16; H, 7.07; N, 5.84.

### 4.4. One pot procedure using sodium carbonate and sodium bicarbonate

The chloroethyl- or chloropropylamine hydrochloride salt (1.10 mmol) was first neutralized with $Na_2CO_3$ or bicarbonate (2 equiv) in MeOH solution. To the solution was added **1** (1.00 mmol) at 0 °C and than at room temperature for 72 h under $N_2$ (TLC analysis indicate the disappearance of the **1** and **3**). The MeOH was removed under reduce pressure, water added, and extracted with $CH_2Cl_2$. Purification of the crude mixture by preparative TLC provided the corresponding product (see Table 1).

**4.4.1. 2,3-Di-[*N*-(2-chloroethyl)-5-methylpyrrol-1-yl]-1,4-diphenylbutane-1,4-dione (5a).** Obtained as an orange gum. $\nu_{max}$: 1675 $cm^{-1}$. $\delta$ 7.84 (d, $J$=6.9 Hz, 4H), 7.44 (m, 2H), 7.35 (m, 4H), 6.03 (d, $J$=3.6 Hz, 2H), 5.84 (d, $J$=3.6 Hz, 2H), 5.32 (s, 2H), 3.65 (m, 4H), 3.21 (m, 2H), 2.92 (m, 2H), 2.15 (s, 6H); $^{13}C$ NMR (50 MHz) $\delta$ 198.21, 137.06, 132.53, 130.19, 128.46, 128.23, 125.49, 109.71, 108.02, 50.60, 43.91, 41.49, 12.50; MS (EI) *m/z* 524 (2), 522 (10), 520 (16), 260 (100). HRMS *m/z* calcd for $C_{30}H_{30}Cl_2N_2O_2$, 520.1684; found, 520.1686.

**4.4.2. 2,3-Di-[*N*-(2-chloropropyl)-5-methylpyrrol-1-yl]-1,4-diphenylbutane-1,4dione (5b).** Obtained as an orange crystal, mp 128 °C. $\nu_{max}$: 1670 $cm^{-1}$. $^{1}H$ NMR (200 MHz): $\delta$ 7.85 (d, $J$=6.9 Hz, 4H), 7.44 (m, 2H), 7.38 (m, 4H), 5.98 (d, $J$=3.6 Hz, 2H), 5.78 (d, $J$=3.6 Hz, 2H), 5.33 (s, 2H)

3.45 (t, $J=7.8$ Hz, 4H), 3.38 (m, 2H), 2.14 (s, 6H), 1.85 (m, 2H), 1.36 (m, 2H); $^{13}$C NMR (50 MHz) $\delta$ 198.56, 137.28, 132.40, 129.84, 128.41, 128.29, 125.29, 109.17, 107.38, 50.69, 42.15, 40.12, 33.13, 12.74; MS (EI) *m/z* 552 (0.5), 550 (4), 548 (6), 447 (1), 445 (6), 443 (10), 274 (100), 105 (50). HRMS *m/z* calcd for $C_{32}H_{34}Cl_2N_2O_2$, 548.1997; found, 548.2111.

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19. Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435–438.
20. Crystal data for **5b**: orange prism crystal of $C_{32}H_{34}Cl_2N_2O_2$, $M_W=549.54$, triclinic, space group *P*-1 (#2), $a=10.15$ (1) Å, $b=11.59$ (1) Å, $c=14.06$ (2) Å, $\alpha=98.1$ (1)°, $\beta=93.50$ (10)°, $\gamma=113.99$ (8)°, $V=1483$ (3) Å$^3$, $Z=2$, $D_c=1.230$ g/cm$^3$, $R=0.063$, $R_w=0.055$, GOF=4.01 for 2358 reflections with $I>3.00\ \sigma(1)$. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Center under the following numbers: CCDC-165004.