Selective Synthesis and Utility of One Tripyrrolic Compound and Its Intermediates

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Highly selective syntheses of tri(2,4-dimethyl-3-carbethoxypyrrolyl)-methane 8 and its dipyrrolic intermediate 6 and pyrrolic one 1 are described based on the successful correction of the wrong process for 1 in literature. Tripyrrolic compounds have attracted much attention recently and been developed in diverse fields. 1 was the key intermediate for some tyrosine kinase inhibitors, including newly-launched Sutent®, and most recently we have found 6 was also synthetically useful in the synthesis of 11 that has been discovered as a novel histone deacetylases (HDAC) inhibitor with an IC_{50} value of about 1 μM in our assessments and represents a promising lead for the development of more potent histone deacetylase inhibitors (HDACIs).

Key words pyrrole; aldehyde; histone deacetylase inhibitor (HDACI); simple procedure; heterocycle

The aldehyde function is one of great importance in the chemistry of pyrroles. The combination of trifluoroacetic acid (TFA) and trimethyl or triethyl orthoformate (TOF) has been conveniently used to prepare various pyrrole aldehydes.[1—4)]

2,4-Dimethyl-3-carbethoxypyrrolyl-5-aldehyde (**1**) was the key intermediate in the synthesis of tyrosine kinase inhibitor SU11248 (Fig. 1) that has been launched as Sutent® in U.S. and Europe in 2006 for its potent antiangiogenic and antitumor activity.[5,6)] In addition, **1** was also extremely important for the synthesis of the selective c-Met inhibitors PHA-665752 (Fig. 1) and SU11274, both are clinical candidates from Pfizer.[7)]

Unfortunately, the processes available for it were awfully limited, and its preparation was mainly from the traditional Gattermann–Kochor and Vilsmeier–Haack procedures starting from 2,4-dimethyl-3-carbethoxypyrrole (**2**).[8,9)] However, the both were suffered from low yield and complex by-products hard to be removed. In addition, the synthesis of **2** was very difficult and mainly from decarboxylation of 2,4-dimethyl-3,5-dicarbethoxypyrrole (**3**),[10)] which further limited the utility of the procedures. In a recent report,[11)] the synthesis of **1** starting from **4** using the combination of TFA and TOF afforded a considerable yield although its process was rather complicated than the above-mentioned ones. The title product in the same literature was obtained as a yellow needle after being decolorized with Darco and recrystallized twice from ethanol (Chart 1).

We repeated the process and got a good repetition. Its ^{1}H-NMR clearly showed the corresponding chemical shifts and coupling constants except the integral value for aldehyde group was a little lower than the required, which was commonly encountered in heterocycle chemistry.[12)] However, we suffered from difficulties in its subsequent hydrolysis to its corresponding acid **5** under reflux for over 5 h using high up to 10 eq of sodium hydroxide, while its similar acids could be obtained in high yield readily by selective hydrolysis of the corresponding esters in the presence of one equivalent of sodium hydroxide.[13)] The problem with the hydrolysis was originated from its bad solubility in various concentration and volume of aqueous methanol or ethanol, which led to complex products and left majority of starting material intact. We had to suspect whether **1** was prepared wrongly and characterized incorrectly although its hydrolyzed products contained a little proportion of **5** *via* HPLC-ESI/MS analysis. Subsequently, based on its ^{1}H-NMR and preparation process, its ESI-MS data confirmed our suspect with a set of peaks: 74, 165, 167 and 345 (M^+) characteristic of its dipyrrolic polymer, *i.e.*, bis(2,4-dimethyl-3-carbethoxypyrrolyl)-methene **6** instead of **1**, which in turn successfully elucidated the above so-called "irregular" integral for aldehyde group (Chart 2).

In light of the increasing need of **1**, it is therefore desirable to find satisfactory manufacturing process for **1**. The wrong synthesis of **1** in the literature was carried out at room temperature for 1 h and then the solvent TFA was removed by evaporation, which produced **6** other than **1**. 2-Formylpyrroles condense readily with 2-unsubstituted pyrroles in the presence of acid to form the synthetically useful 2,2′-

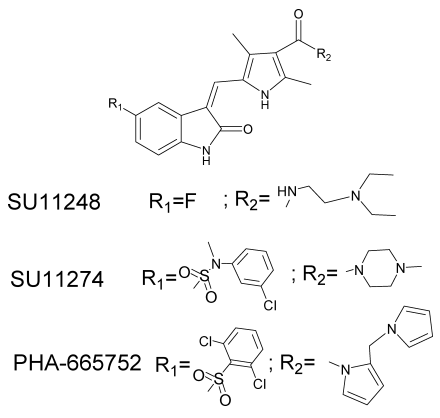

Fig. 1

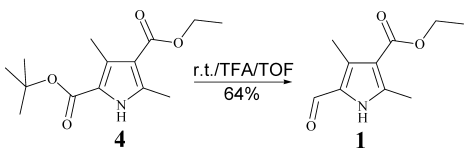

Chart 1

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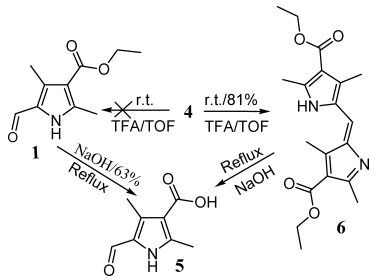

Chart 2

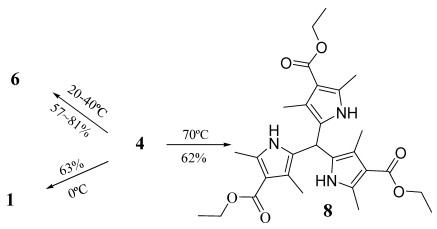

Chart 3

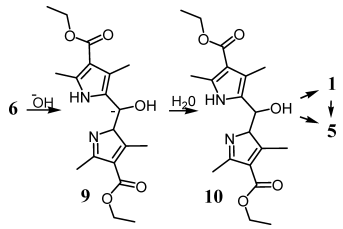

Chart 4

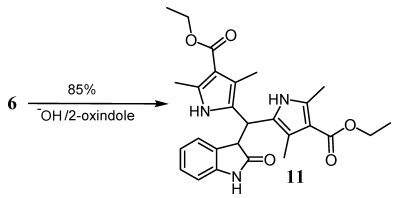

Chart 5

Table 1. The Dependence on Temperature at which **1**, **6** and **8** Were Formed

Entry	Temperature (°C)	Reaction time	Product	Yield (%)
1	0	1 h	**1**	63%
2	20	1 h	**6**	81%
3	40	1 h	**6**+**8**	57+20%
4	70	2—10 min	**8**	62%

dipyrromethene salts.[14] From the synthesis of **6** we were able to hazard a guess that its formation was somehow connected with the temperature involved in the reaction and **6** might be formed based on the self-condensation of **1**. To investigate this hypothesis, an experimental design as summarized in Table 1 was set up. From the results it was evident that the temperature of reaction played a crucial role in the synthesis of **1**.

The reaction provided pure aldehyde **1** instead of **6** at 0 °C. Besides, a survey of interesting phenomena have also been observed and investigated in the process of adjusting the reaction temperature. At room temperature, the reaction produced a major proportion of dipyrrolic compound **6** (81%). **6** was still the major product (57%) while the reaction temperature was increased to 40 °C, interestingly, a tri(2,4-dimethyl-3-carbethoxypyrrolyl)-methane **8** could also be separated in 20% yield. When the reaction temperature was elevated to 70 °C, a high yield of **8** could be yielded up to 62% (Chart 3).

8 is a previously-unreported tripyrrolic compounds to the best of our knowledge. Recently, tripyrrolic compounds have attracted much attention and been developed in diverse fields, such as in asymmetric synthesis,[15] synthesis of pyrrole-substituted porphyrins,[16,17] bis(tripyrrolyl)cryptands binding difunctional guest molecules[18] and dimensional probes for anion-binding event.[19] Highly selective one-pot synthesis of tri(2,4-dimethyl-3-carbethoxypyrrolyl)methane might be easily extended to preparation of its derivatives.

In addition, what interested us more is that **5** was not only able to be hydrolyzed from **1**, but also one product in the hydrolysis of **6**. It suggested that double bond of **6** was highly reactive under basic conditions, the formation of **5** may experience the following successive transformations (Chart 4).

Over these years, there have been considerable efforts in the identification of receptor tyrosine kinase inhibitors (RTKIs) as novel anticancer drugs in the past several years, and 2-oxindole-based receptor RTKIs have achieved great successes, such as the above-mentioned SU11248, SU11274 and PHA-665752 that are all 3,5-dimethyl-(pyrrol-2-yl)methylene-1,3-dihydro-2*H*-indol-2-one compounds. However, recent studies show that the double bond bound to oxindole acting as a bridge is not indispensable and many novel potent RTKIs have diverse structures.[20] **6** formed the basis for certain well-known routes to porphyrins including the regiospecific synthesis.[8] However, the investigation into the synthesis and utility of 2-oxindole-binding dipyrrolic compounds has never been conducted. The high reactivity of **6** under basic conditions reminded us it may act as useful electrophilic reagent. Most recently we have found **6** was synthetically useful in the synthesis of **11** (Chart 5) and its inhibitory activity for many protein targets including RTKs has also been assayed. To our disappointment, it has no obvious inhibitory effect on many RTKs, including VEGFR, EGFR, FGFR and PDGFR. Unexpectedly, it has been discovered as a new histone deacetylases (HDACs) inhibitor with an IC_{50} value of about 1 μM in our assessments. HDACs play a critical role in gene transcription and have become a new target for the discovery of drugs against cancer. More interestingly, **11** was completely different from the existing HDAC inhibitors and represents a promising lead compound for the development of more potent ones.

In conclusion, we have developed a highly efficient and convenient method for the selective preparation of tri(2,4-dimethyl-3-carbethoxypyrrolyl)-methane **8** and its pyrrolic intermediates **6** and **1** using **4**. **4** was readily available in high yield by Knorr reaction starting with *t*-butyl-3-oxobutyrate, experiencing the successive oximation, reduction and condensation. They are all useful in various fields, especially in the synthesis of novel anti-cancer drugs and more importantly, their diverse derivatives can be developed through fur-

ther investigations into broadening the scope and synthetic applications of this efficient reaction.

Experimental

All solvents were used as obtained from commercial suppliers. ^{1}H-NMR was recorded at Bruker Avance 400 in DMSO-d_6 and chemical shifts were expressed in parts per million (δ) relative to tetramethylsilane. Melting points were uncorrected. Mass spectroscopy (MS) was performed at Micromass ZabSpec. TLC plates coated with silica gel were run in an ethyl acetate/hexane mixture and spots were developed in ultraviolet.

The processes for **1**, **6** and **8** were the same except the reaction temperature and time.

General Process for **1**, **6** and **8**: Triethyl orthoformate (1.2—1.6 eq) was added all at once to a stirred solution of **4** (1 eq) and TFA (15—20 eq). The mixture was stirred for a period of time under the temperature as shown in Table 1. The reaction mixture was then poured into ice (for **1**) or condensed to dryness (for **6** and **8**). The resultant products were flash chromatographed (silica gel, hexane : EtOAc) and recrystallized with methanol.

For **8**: Red solid, yield: 62%; mp: 173—175 °C; micro-analysis C, 65.18; H, 7.30; N, 7.96. $C_{28}H_{37}N_3O_6 \cdot 0.2CH_3OH$ requires: C, 65.37; H, 7.35; N, 8.12; TLC: *Rf*=0.18 (silica gel GF_{254}; eluent: Hexane/EtOAc, 2/1) and the dot of product on TLC will be increasingly gone yellow while long standing in open air at room temperature; δ_H [400 MHz/$(CD_3)_2SO$/TMS]: 10.32 (s, 3H), 5.39 (s, 1H), 4.13 (6H, q, *J*=8 Hz), 2.35 (s, 9H), 1.95 (s, 9H), 1.23 (9H, t, *J*=8 Hz), CH_3OH (5.67, 0.31H; 3.32, 0.97H); FAB-MS: *m*/*z* (%)=512.2 (M^++1), 345.2 [M^+-(2,4-dimethyl-3-carbethoxypyrrolyl)].

For **6**: Yellow needle crystalline, yield: 81%; mp: 196 °C; TLC: *Rf*=0.67 (silica gel GF_{254}; Hexane/EtOAc, 5/2), yellow dot under visible light; δ_H [400 MHz/$CDCl_3$/TMS]: 13.92 (s, 2H), 7.46 (s, 1H), 4.33—4.37 (4H), 2.79 (s, 6H), 2.66 (s, 6H), 1.38—1.42 (6H); ESI: *m*/*z* (%)=345 (M^+).

For **1**: White solid, yield: 63%; mp: 163—164 °C; TLC: *Rf*=0.49 (silica gel GF_{254}; hexane/EtOAc, 5/2), UV; δ_H [400 MHz/$CDCl_3$/TMS]: 12.19 (s, 1H), 9.62 (s, 1H), 4.18 (2H, q, *J*=7.2 Hz), 2.46 (s, 3H), 2.42 (s, 3H), 1.28 (3H, t, *J*=7.2 Hz).

For **11**: A reaction mixture of oxindole (40 mg, 0.3 mmol), **6** (120 mg, 0.36 mmol) and triethylamine (2 drops) in absolute ethanol (5 ml) was stirred in 100 °C for 30 min. The mixture was concentrated and and the residue was recrystallized with ethanol (95%) to give cololess solid (0.122 g, 85%). TLC: *Rf*=0.67 (silica gel GF_{254}; Hexane/EtOAc, 1/1), the dot went yellow while long standing; $C_{27}H_{31}N_3O_5$, found: C, 67.47; H, 6.60; N, 8.62, Calcd: C, 67.76; H, 6.57; N, 8.83; EI: *m*/*z* (%)=477 (M^+, weak), 344 (M^+-oxindole), 133 (oxindole$^+$); δ_H [400 MHz/$(CD_3)_2SO$/TMS]: 10.95 (s, 1H), 10.50 (s, 1H), 10.33 (s, 1H), 7.14 (t, 1H, *J*=7.2 Hz), 6.75 (t, 1H, *J*=7.2 Hz), 6.72 (dd, 2H, *J*=4.0, 14.8 Hz), 4.44 (d, 1H, *J*=3.6 Hz), 4.13 (d, 1H, *J*=3.6 Hz), 4.07 (m, 4H), 2.45 (s, 3H), 2.37 (s, 3H), 1.94 (s, 3H), 1.86 (s, 3H), 1.22 (m, 6H).

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