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Iron(III) Salt-Catalyzed Nazarov Cyclization/Michael Addition of Pyrrole Derivatives

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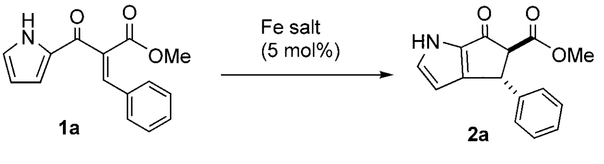
Abstract: The Nazarov cyclization of two types of pyrrole derivatives was effectively catalyzed by 5 mol% alumina-supported iron(III) perchlorate [$Fe(ClO_4)_3\cdot Al_2O_3$] which provided the desired cyclization with high *trans* selectivity in good to excellent yield. The cyclized product was next reacted with a vinyl ketone in the presence of the same iron salt to afford the corresponding Michael product. A sequential type Nazarov/Michael reaction of pyrrole derivatives has also been accomplished; the synthetic route to 4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one derivative **5** or 5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one derivative **6** has thus been established using a very economical iron catalyst.

Keywords: iron(III) salts; Michael addition; Nazarov cyclization; pyrroles; sequential reactions

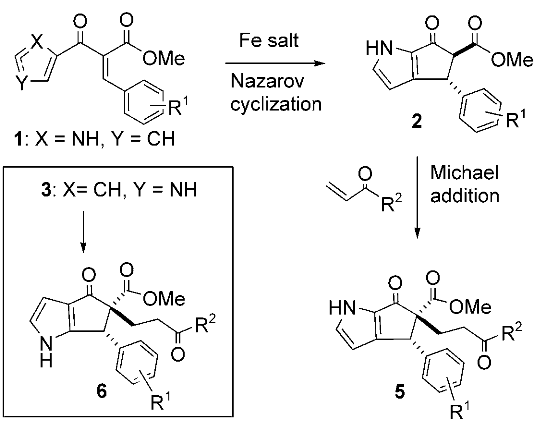
Iron is one of the most abundant and environmentally friendly metals on the earth and several groups have reported various types of iron metal-catalyzed organic transformations during the past decades.[1] We have also been investigating the possibility of iron-catalyzed reactions and developed several of them, i.e., the intramolecular cyclization of cyclopropane dithioacetals,[2] the [2+2]cycloaddition of *trans*-anethol,[3] the [2+3]type cycloaddition of styrene derivatives with 1,4-benzoquinone,[4] the 1,4-addition of β-keto esters to vinyl ketones,[5] the enantioselective Michael addition of thiols to α,β-unsaturated carbonyl compounds,[6] Friedel–Crafts type alkylation of indoles[7] or pyrroles[8] with vinyl ketones, and, most recently, the Nazarov type cyclization of thiophene derivatives.[9]

Nazarov cyclization is a very versatile method for the synthesis of five-membered carbocycles, and it is well known that several Lewis or Brönsted acids promote this reaction.[9,10,11] Frontier, Eisenberg and coworkers recently reported the Ir(III) complex-catalyzed tandem Nazarov cyclization/Michael reaction.[12] However, the Nazarov cyclization of pyrrole derivatives is not popular,[13] although the pyrrole moiety is very common in many biologically active or functional molecules. The reason the reaction is not popular is assumed to be that pyrroles are easily polymerized in the presence of strong Lewis acid such as iron(III) chloride.[1] We recently established that pyrrole reacted with vinyl ketones in the presence of 3 mol% of iron(II) tetrafluoroborate [($Fe(BF_4)_2\cdot 6H_2O$)] or alumina-supported iron(III) perchlorate ([$Fe(ClO_4)_3\cdot Al_2O_3$)][3,8] to give multi-point-alkylated products.[8] Most notably, the 4,5-dialkylated product was obtained in good yield when 2-acetylpyrrole was reacted with an excess amount of vinyl ketones.[8] Based on the results, we hypothesized that the tandem or sequential type of Nazarov cyclization and Michael addition of pyrrole derivatives might be possible using our iron salt catalyst system. Here we report an efficient route to access 4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one derivative **5** or 5,6-dihydrocyclopenta[*b*]-pyrrol-4(1*H*)-one derivative **6** through a step-by-step or sequential reaction pathway using an economical iron salt catalyst as illustrated in Scheme 1.

We initially attempted to optimize reaction conditions of Nazarov cyclization of **1a** to access **2a** [(Eq. (1)]. Typically, the reaction was carried out as follows:



(1)



Scheme 1. Working hypothesis for the Fe salt-catalyzed sequential type Nazarov cyclization/Michael addition.

5 mol% of iron salt and **1a** were mixed in a solvent at 60 °C and product **2a** was isolated by silica gel thin layer chromatography (TLC). We performed the reaction using various iron salts [($FeCl_2$, $FeBr_2$, $Fe(acac)_2$, $Fe(OAc)_2$, $Fe(ClO_4)_2{\cdot}6H_2O$, $Fe(OTf)_2$, $FeCl_3$, $Fe(ClO_4)_3{\cdot}nH_2O$, and $Fe(acac)_3$)] and solvents [toluene, tetrahydrofuran (THF), 1,4-dioxane, acetonitrile, dichloroethane, MeOH, H_2O and ionic liquids]. As anticipated, the desired Nazarov cyclization proceeded very smoothly and cyclized product **2a** was obtained using an iron salt as catalyst; several important results are summarized in Table 1.

We first tested the reaction using $Fe(ClO_4)_3{\cdot}Al_2O_3$[3,8] in CH_3CN because CH_3CN worked as the best solvent for the iron salt-catalyzed alkylation of 2-acetylpyrrole[8] or indole.[7] However, the reaction proceeded very slowly and **2a** was obtained in poor yield (entry 1); no improvement was observed even though the reaction was continued for several days. Fortunately, the desired **2a** was obtained in excellent yield (92%) when the reaction was carried out in dichloromethane (CH_2Cl_2) as solvent (entry 2). An X-ray crystallographic analysis of the major cyclized product **2a** revealed the *trans* relationship between the α-carbomethoxy group and the β-phenyl group (Figure 1).[14] Interestingly, an excellent yield (94%) was recorded when the reaction was carried out in an ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethyl)sulfonylamide ([Bmim] [NTf_2]), although a long reaction time was required to complete the reaction (entry 6). Because avoidance of the use of haloalkane is necessary from environmental aspects, this feature might be quite important in future. $Fe(BF_4)_2{\cdot}6H_2O$ worked as catalyst when the reaction was carried out under air conditions, and a prolonged reaction time (7 days) was required to complete the

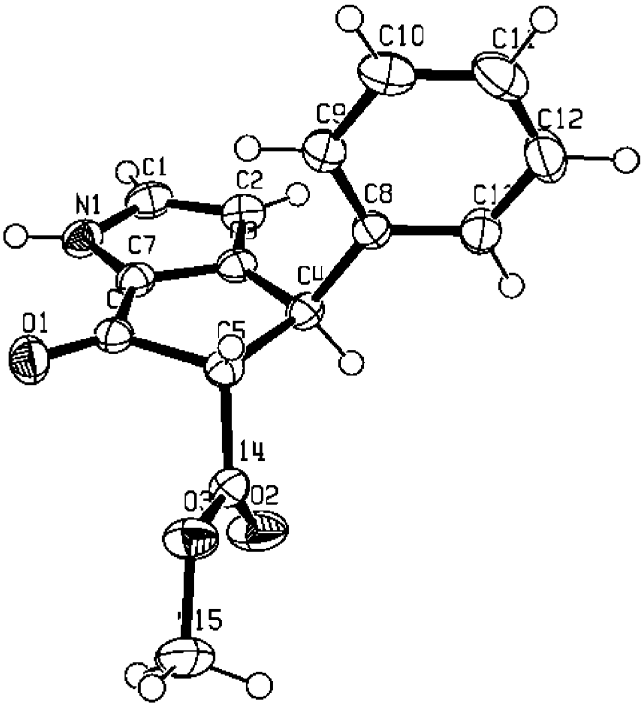


Figure 1. ORTEP view of *trans*-**2a**.

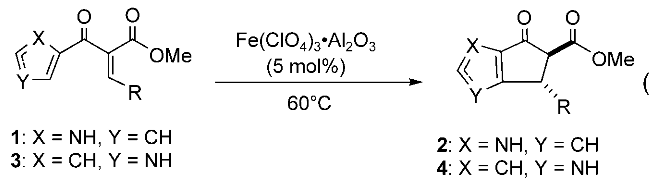
Table 1. Fe salt-catalyzed Nazarov cyclization of **1a**.

Entry	Fe salt catalyst	Solvent	Temp./time	Yield[a] of **2a**	Ratio[b] *trans*:*cis*
1	$Fe(ClO_4)_3{\cdot}Al_2O_3$	CH_3CN	60 °C/22 h	45% (49%)[c]	–
2	$Fe(ClO_4)_3{\cdot}Al_2O_3$	CH_2Cl_2	60 °C/4 h	92%	20:1
3	$Fe(ClO_4)_3{\cdot}Al_2O_3$	1,2-dichloroethane	80 °C/6 h	84%	25:1
4	$Fe(ClO_4)_3{\cdot}Al_2O_3$	toluene	60 °C/22 h	70% (19%)[c]	27:1
5	$Fe(ClO_4)_3{\cdot}Al_2O_3$	toluene	100 °C/4 h	84%	20:1
6	$Fe(ClO_4)_3{\cdot}Al_2O_3$	[Bmim] [NTf_2]	60 °C/4 days	94%	23:1
7	$FeCl_3$	CH_2Cl_2	60 °C/48 h	70%	27:1
8	$Fe(BF_4)_2{\cdot}6H_2O$	CH_2Cl_2	60 °C/7 d	77% (11%)[c]	17:1
9	$Fe(ClO_4)_3{\cdot}Al_2O_3$	THF	60 °C/22 h	<30% (63%)[c]	–
10	$Fe(ClO_4)_3{\cdot}Al_2O_3$	MeOH, H_2O	60 °C/22 h	0% (100%)[c]	–

[a] Isolated yield by silica gel column chromatography.
[b] The ratio was determined by 500 MHz ^1H NMR.
[c] Recovered yield of unreacted substrate **1a**.

reaction (entry 8). Iron(III) chloride also worked as catalyst (entry 7), although the result was less satisfactory compared to that of the $Fe(ClO_4)_3 \cdot Al_2O_3$-catalyzed reaction. No reaction took place when THF, MeOH or H_2O was used as solvent (entries 9 and 10). Therefore, use of a non-polar solvent was essential for this reaction. It was found that the Brönsted acid $HClO_4$ 10 mol% also worked as catalyst but the yield of **2a** was poor (less than 30%) due to the formation of an unidentified by-product. Therefore it was concluded that the combination of $Fe(ClO_4)_3 \cdot Al_2O_3$ and CH_2Cl_2 was the most promising condition for the intended cyclization reaction of **1a**. It should be noted that the reaction required no argon atmosphere and proceeded smoothly under dried air conditions. We tried to improve the chemical efficiency of the reaction by performing it at a higher reaction temperature (100 °C) in [Bmim] [NTf_2] solvent, but a significant reduction of the chemical yield was recorded because of the formation of the decarboxylated compound 4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one. Although this difficulty was expected to be solved by optimization of the design of the ionic liquids, we decided to optimize the further reaction conditions using CH_2Cl_2 as solvent at this stage.

We next examined the scope and limitations of the iron salt-catalyzed reaction with the various types of pyrrole derivatives **1**[15] or **3**[15] [(Eq. (2)]. All reactions were carried out with 5 mol% $Fe(ClO_4)_3 \cdot Al_2O_3$ in CH_2Cl_2 at 60 °C under dried air conditions, and the reaction products were isolated by silica gel TLC (Table 2). The reaction of substrates **1b**, **1c**, **1l**, **1o**, **1q** which possess an electron-donating group on the benzene ring, smoothly proceeded and gave the corresponding products in excellent isolated yield (entries 1, 2, 11, 14, and 15).



(2)

Although a reduced reaction rate was observed, the desired products were also obtained in excellent yields for substrates **1d**, **1e**, **1f**, **1g**, **1h**, **1m**, and **1n** which have an electron-withdrawing group, such as a halogen, trifluoromethyl or cyano group on the phenyl group (entries 3–7, 12 and 13). On the other hand, reactions using substrates **1q**, **1r**, and **1s** which have an aliphatic group at R^1, gave somewhat decreased yields (entries 16–18). To our delight, the cyclization proceeded very smoothly when 3-substituted pyrrole derivative **3a** was used as substrate and the desired product **4a** was obtained in 91% yield after just 1 h reaction (entry 19). An excellent chemical yield of **4a** was also recorded even when the amount of catalyst was reduced to 0.1 mol% (entry 20). The synthesis of 4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one derivative **5** or 5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one derivative **6** was thus accomplished using a very economical catalysis system.

Table 2. Fe salt-catalyzed Nazarov cyclization of **1** or **3**.[a]

Entry		Substrate (R)	Time	Yield[b] of **2** or **4**	Ratio[c] *trans*:*cis*
1	**1b**	4-MeO-C_6H_4	4 h	92%	19:1
2	**1c**	4-Me-C_6H_4	18 h	93%	22:1
3	**1d**	4-NO_2-C_6H_4	7 days	77%	14:1
4	**1e**	4-Cl-C_6H_4	19 h	88%	14:1
5	**1f**	4-CN-C_6H_4	60 h	90%	19:1
6	**1g**	4-F-C_6H_4	18 h	85%	23:1
7	**1h**	4-CF_3-C_6H_4	36 h	82%	18:1
8	**1i**	3,4,5-$(MeO)_3C_6H_2$	90 h	90%	25:1
9	**1j**	2,4,6-$(MeO)_3C_6H_2$	3 h	75%	22:1
10	**1k**	3-MeO-C_6H_4	55 h	84%	19:1
11	**1l**	3-Me-C_6H_4	17 h	91%	78:1
12	**1m**	3-CF_3-C_6H_4	64 h	82%	18:1
13	**1n**	2-CF_3-C_6H_4	76 h	80%	27:1
14	**1o**	2-MeO-C_6H_4	2 h	97%	34:1
15	**1p**	1-naphthyl	5 h	97%	19:1
16	**1q**	*c*-hexyl	3 days	79%	$>99:<1$
17	**1r**	Et	12 h	52%	30:1
18	**1s**	*i*-Pr	18 h	84%	$>99:<1$
19	**3a**	C_6H_5	1 h	91%	28:1
20[d]	**3a**	C_6H_5	17 h	92%	28:1

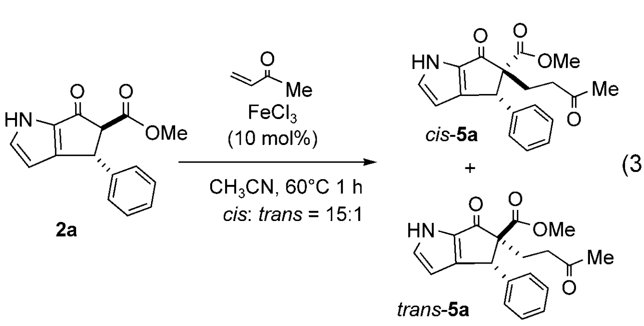
[a] *Reaction conditions:* **1** or **3** (0.25 mmol), $Fe(ClO_4)_3 \cdot Al_2O_3$ (0.0125 mmol), CH_2Cl_2 (0.5 mL).

[b] Isolated yield by silica gel column chromatography.

[c] The ratio was determined by 500 MHz ^{1}H NMR.

[d] 0.1 mol% of the catalyst was used.

We next tested Michael reaction of **2a** in the presence of $Fe(ClO_4)_3 \cdot Al_2O_3$ in CH_3CN solvent and found the desired product was obtained in 86% yield as a white powder [(Eq. (3)]. Interestingly, the chemical shift of the methoxy group was observed at 3.0 and 3.8 ppm at a ratio of 15:1 in the ^{1}H NMR spectrum. An X-ray crystallographic analysis of the major product **5a** (*cis*-**5a**) clearly showed the reason that the



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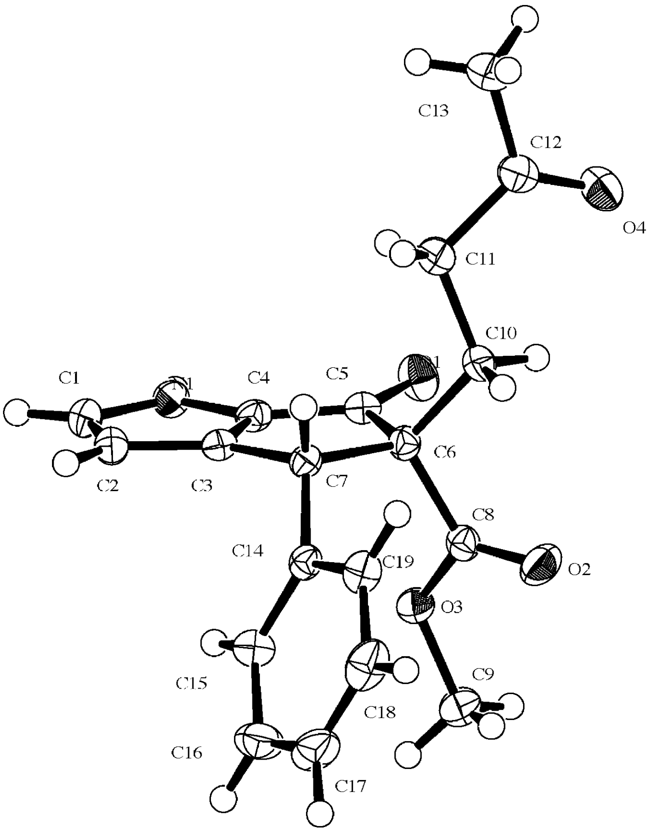
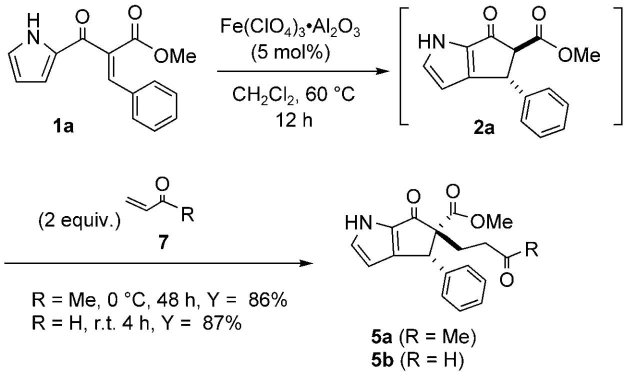


Figure 2. ORTEP view of *cis*-**5a**.

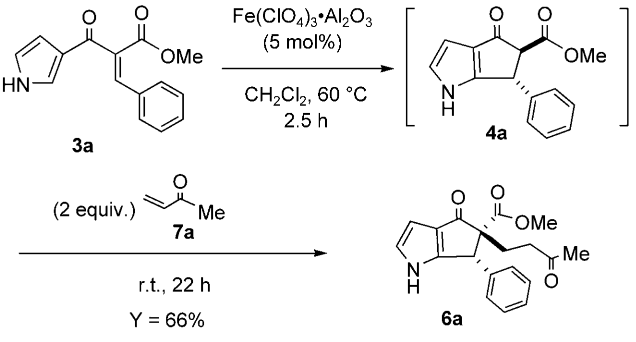


Scheme 2. $Fe(ClO_4)_3 \cdot Al_2O_3$-catalyzed sequential type Nazarov/Michael reaction of pyrrole derivative **1a**.

chemical shift of the methoxy group appeared in such a high field region around 3.0 ppm.[16] As can be seen in Figure 2, the methoxy group locates just behind the phenyl group; therefore, the signal of the methoxy group moves to a high field region due to the shield effect by the phenyl group. It was thus concluded that the Michael reaction proceeds with *trans* selectivity and the methoxycarbonyl group located at the *cis* position from the β-phenyl group. Although this Michael reaction was initially accomplished using CH_3CN as solvent,[5] we discovered that the reaction also smoothly took place in CH_2Cl_2; this made it possible to realize the Nazarov cyclization and subsequent Michael reaction using a one-pot reaction system. Methyl 1,4,5,6-tetrahydro-6-oxo-5-(3-oxobutyl)-4-phenylcyclopenta[*b*]pyrrole-5-carboxylate (**5a**) was obtained in 88% yield through this sequential type Nazarov/Michael reaction. The reaction was carried out as follows: pyrrole derivative **1a** was treated with 5 mol% of $Fe(ClO_4)_3 \cdot Al_2O_3$ in CH_2Cl_2 at 60 °C with stirring for several hours and the reaction course was monitored by silica gel TLC. The reaction mixture was cooled to room temperature after confirmation that the starting **1a** had been consumed and **2a** produced, then 2 equiv. of 3-buten-2-one (**7a**) or acrolein (**7b**) were added to the reaction mixture at 0 °C or room temperature. The desired Michael adduct **5a** or **5b** was obtained in 86% or 87% yield, respectively (Scheme 2). Unfortunately, a tandem type reaction was unsuccessful if a mixture of **1a** and **7a** was treated with the iron salt catalyst because the initial step required 60 °C to complete the reaction, while significant polymerization of **7a** took place under these high temperature conditions.

The sequential type Nazarov cyclization/Michael reaction was also accomplished when pyrrole derivative **3a** was subjected to the reaction: product **6a** was obtained in 66% yield, although further alkylated products were formed as by-products (Scheme 3).[15] Interestingly, it was found that the Michael reaction of **4a** was slower than that of **2a**, although the Nazarov cyclization of **3a** proceeded faster than that of **1a**. Since the carbomethoxy group of **6a** was observed at 3.0 ppm in the ^1H NMR spectrum, the same *cis* relationship of the α-carbonyl group with the β-phenyl group of **6a** was suggested. This assignment was supported by the results of PM3 calculation of two possible stereoisomers of *cis*-**6a** and *trans*-**6a**. The heat of formation of the optimized structure of *cis*-**6a** was suggested to be $-420.036\ kJ\,mol^{-1}$, while that of *trans*-**6a** was $-417.878\ kJ\,mol^{-1}$.[15]

In conclusion, we have established an iron(III) salt-catalyzed Nazarov cyclization of two types of pyrrole



Scheme 3. $Fe(ClO_4)_3 \cdot Al_2O_3$-catalyzed sequential type Nazarov/Michael reaction of pyrrole derivative **3a**.

derivatives. The reaction was effectively catalyzed by 5 mol% $Fe(ClO_4)_3{\cdot}Al_2O_3$ and the desired products were obtained in good to excellent yields. Since the cyclized products reacted with vinyl ketones to give the corresponding Michael adducts in the presence of the same iron salt catalyst, a sequential type Nazarov/Michael reaction has been accomplished. It should be emphasized that the reaction is accomplished by a very economical and environmentally friendly iron salt as catalyst and requires no tedious argon atmospheric conditions. Further investigation of asymmetric Nazarov cyclization using a chiral iron catalyst is now in progress by our group.

Experimental Section

Synthesis of 5b through the Sequential Type Nazarov Cyclization/Michael Reaction

To a mixture of $Fe(ClO_4)_3{\cdot}Al_2O_3$[3,8] (60 mg, 8.8 wt% for Fe^{3+}, 0.0125 mmol) in CH_2Cl_2 (0.5 mL) was added **1a** (64 mg, 0.25 mmol) at room temperature and the mixture was stirred at 60 °C for 12 h. The reaction mixture was cooled to room temperature after confirmation that the starting **1a** had been consumed and **2a** produced, then 2 equiv. of but-3-en-2-one (**7a**) were added to the reaction mixture at 0 °C and stirred for 48 h at the same temperature. The reaction was quenched with water, and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by evaporation under vacuum. The residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 1/1) to give **5a** as a white solid; yield: 70 mg (0.22 mmol, 86%; **5a** (*cis*): mp 251–253 °C (recrystallized from $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.18$ (3H, s), 2.41–2.48 (1H, m), 2.57–2.65 (2H, m), 2.80–2.87 (1H, m), 3.04 (3H, s), 4.35 (1H, s), 6.15–6.17 (1H, m), 7.14–7.16 (2H, m), 7.23–7.29 (2H, m), 7.42–7.44 (1H, m), 10.94 (1H, brs, N-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.69$, 30.01, 38.49, 51.00, 51.39, 71.44, 106.61, 127.51, 127.94, 128.86, 134.05, 134.18, 138.14, 152.62, 170.68, 188.32, 207.93; IR (KBr): $\nu = 3293$, 1740 (CO), 1711 (CO), 1680 (CO), 1449, 1398, 1381, 1269, 1219, 706 cm^{-1}.

Compound **5b** was also prepared through the same route in 87% yield from **1a**.

Supporting Information

Detailed experimental procedures and ^1H NMR and ^{13}C NMR spectral data for new compounds (**2a–2s**, **4a**, **5a**, **5b**, and **6a**) are available in the Supporting Information.

Acknowledgements

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[14] CCDC 706556 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[15] For details of the sequential type Nazarov/Michael reaction, and the preparation of substrates **1a**–**1s**, and **3a**, see the Supporting Information.

[16] CCDC 706750 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.