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Synthesis of Methanes Having Four Different Carbon Substituents Utilizing Indium-Catalyzed Cleavage of Carbon–Pyrrolyl Bonds

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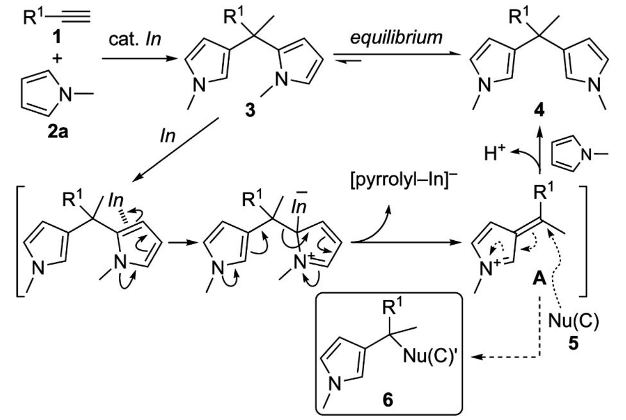
A pyrrolyl group bound to an sp^3 carbon atom in *gem*-dipyrrolylalkanes was found to be successfully replaced by a certain range of carbon nucleophiles in the presence of an indium catalyst. The reaction can also be performed efficiently as a three-component assembly of alkynes, pyrroles, and carbon nucleophiles in one batch. The strategy is highly useful to synthesize methanes having four different carbon substituents.

Introduction

Under acidic conditions, tertiary alkyl groups are well known to transfer between aromatic rings by C(sp^3)–C(aryl) bond cleavage–bond formation sequences through some cationic species.[1,2] In this context, the *t*Bu group on aromatic rings has played a crucial role as a "positional protective group" to direct incoming electrophiles. Thus far, however, the *t*Bu group has been disposed of after the transalkylation to other aromatic compounds.[3] To the best of our knowledge, such cleavage reactions have been utilized only for synthesis of aromatic compounds with regioselectively introduced substituents. We envisaged that in situ trapping of the released tertiary alkyl groups with carbon nucleophiles would generate quaternary carbon centers connected with all carbon substituents.

We have reported that indium triflate [In(OTf)$_3$, Tf = SO$_2$CF$_3$] catalyzes the double addition of *N*-methylpyrrole (**2a**) to alkynes **1**, giving isomeric mixtures of *gem*-dipyrrolylalkanes (DPAs) [Scheme 1, In(OTf)$_3$ = *In*].[4,5] Under indium catalysis, α,β′-adduct **3** readily isomerizes to β,β′-isomer **4**, in which cationic species **A** was proposed to be an intermediate.[2a] Herein we disclose the first carbon–carbon bond-forming reaction through C(sp^3)–C(pyrrolyl) bond cleavage followed by capture of **A** with carbon nucleophiles **5**. This provides methanes **6** having four different carbon substituents, one of which is a β-pyrrolyl group.[6]



Scheme 1. Working hypothesis for trapping of intermediate **A** with **5**.

Results and Discussion

In order to verify our working hypothesis, we first tested the reaction of 2,2-bis(*N*-methylpyrrol-3-yl)octane (**4a**)[7] with 2-methylfuran (**5a**) (Table 1). Thus, treatment of **4a** and **5a** with In(OTf)$_3$ (10 mol-%) in 1,4-dioxane at 85 °C for 1.5 h gave 2-(5-methylfuran-2-yl)-2-(*N*-methylpyrrol-3-yl)octane (**6a**) in 80 % yield (Table 1, Entry 1).[8–10] Notably, neither α-pyrrolyl isomer **7a** nor double substitution product **8a** was produced. DPAs **4b**–**4e** having other alkyl groups, including bulkier secondary and tertiary ones, at the quaternary carbon center similarly reacted with **5a** (Table 1, Entries 2–5). Interestingly, 1,1,1-triarylethanes **6f** and **6g** having three different aryl groups can be readily prepared, where aryl moieties such as the phenyl and

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thienyl groups do not act as leaving groups (Table 1, Entries 6 and 7). The reaction of **4a** with 2-methoxythiophene (**5b**) also mainly gave monothienyl product **6h**,[11] but a small amount of **8b** was produced through double substitution (Table 1, Entry 8). Importantly, stepwise replacement of the two pyrrolyl groups of **4** also was found to be feasible in this strategy. For example, **6a**, which has been synthesized in Entry 1 of Table 1, reacted with **5b** to give 2-furyl-2-thienyloctane **9** [Equation (1)]. The potential of this method can be demonstrated by using carbon nucleophiles other than heteroarenes. The introduction of an allyl or cyano group was thus achieved by the reaction of **4a** with tetraallyltin (**5c**) or trimethylsilyl cyanide (**5d**), respectively [Equations (2) and (3)]. In the reaction of **4c** with 4-vinylanisole (**5e**), two carbon–carbon bonds were formed in one batch, where a benzylic cation generated after nucleophilic attack of the C=C bond of **5e** is likely to accept the α-position of the remaining pyrrolyl group [Equation (4)]. These results direct us toward further extension of the scope of nucleophiles, and thus are quite promising.

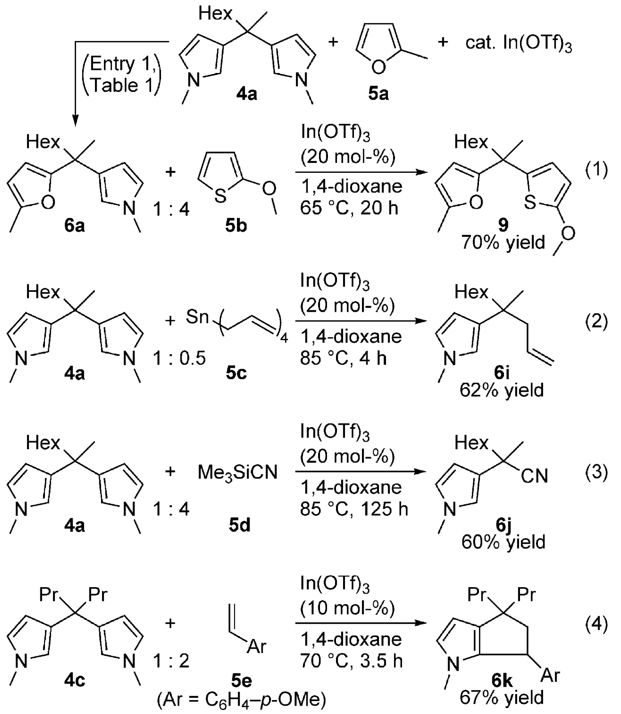
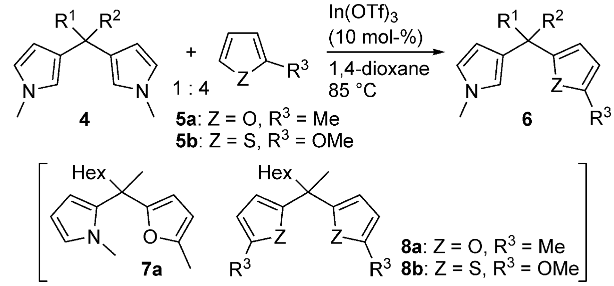


Table 1. $In(OTf)_3$-catalyzed reaction of DPAs with carbon nucleophiles **5**.[a]

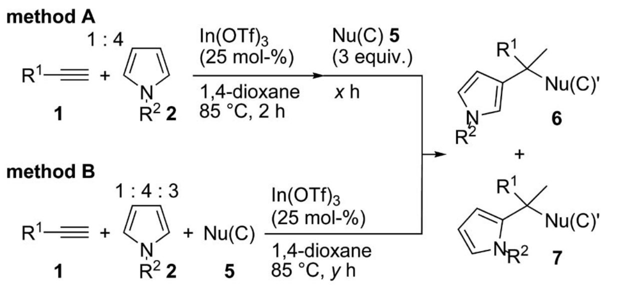


Entry	R^1	R^2	**5**	*t* [h]	Yield [%] of **6**[b]
1	Hex	Me (**4a**)	**5a**	1.5	80 (**6a**)
2[c]	Me	Me (**4b**)	**5a**	4	78 (**6b**)
3	Pr	Pr (**4c**)	**5a**	1.5	72 (**6c**)
4	*i*Pr	Me (**4d**)	**5a**	2.5	64 (**6d**)
5	*t*Bu	Me (**4e**)	**5a**	5	73 (**6e**)
6	Ph	Me (**4f**)	**5a**	18	72 (**6f**)
7[d]	3-thienyl	Me (**4g**)	**5a**	4	78 (**6g**)
8[d,e]	Hex	Me (**4a**)	**5b**	1.5	49 (**6h**)

[a] Reaction conditions: **4** (0.13 mmol), **5** (0.52 mmol), $In(OTf)_3$ (13 μmol), 1,4-dioxane (1.0 mL). [b] Isolated yield based on **4**. [c] Performed at 60 °C. [d] Performed in 1,4-dioxane (0.35 mL). [e] Compound **8b** also was generated in 4% yield.

The procedure requiring the presynthesis of the DPAs can be modified to a more simple protocol, which is a one-pot reaction without the isolation of the DPAs (Table 2). Treatment of 1-octyne (**1a**) and *N*-methylpyrrole (**2a**) with $In(OTf)_3$ as a catalyst at 85 °C for 2 h, followed by the addition of 2-methylfuran (**5a**) gave **6a** in a good yield, though α-isomer **7a** was slightly co-produced (Table 2, Entry 1; method A).[12] The one-pot reaction can be performed also by a different procedure, shown as method B in Table 2. Thus, simultaneous treatment of **1a**, **2a**, **5a**, and a catalytic amount of $In(OTf)_3$ at 85 °C for 2.5 h gave the mixture in 62% yield with the same ratio (Table 2, Entry 2; method B). To the best of our knowledge, this is the first demonstration of the assembly of alkynes and two different heteroarenes, which can be regarded as their substrate-selective addition to C≡C bonds. Aliphatic terminal alkynes having an ace-

Table 2. $In(OTf)_3$-catalyzed three-component reaction of alkynes, pyrroles, and carbon nucleophiles.[a]



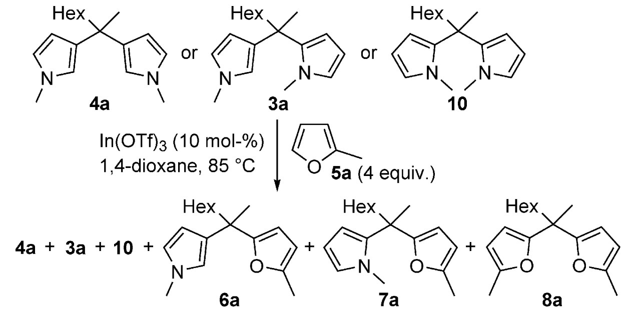
Entry	R^1	R^2	**5**[b]	method, *t* [h]	Yield [%][c] (**6**/**7**)[d]
1	Hex	Me	**5a**	A, *x* = 2.5	71 (97:3)
2	Hex	Me	**5a**	B, *y* = 2.5	62 (97:3)
3	$AcO(CH_2)_3$[e]	Me	**5a**	A, *x* = 12	58 (98:2)
4	$AcO(CH_2)_3$[e]	Me	**5a**	B, *y* = 18	50 (98:2)
5	$NC(CH_2)_3$	Me	**5a**	A, *x* = 12	50 (98:2)
6	*p*-$MeOC_6H_4$	Me	**5a**	A, *x* = 12	51 (96:4)
7	3-thienyl	Me	**5a**	A, *x* = 7	56 (96:4)
8	Hex	Bn[f]	**5a**	A, *x* = 0.5	72 (>99:<1)
9	Hex	*t*Bu	**5a**	A, *x* = 2.5	70 (>99:<1)
10[g]	Hex	Ph	**5a**	A, *x* = 0.5	57 (>99:<1)
11[h]	$CH_3(CH_2)_9$	Me	**5d**[i]	A, *x* = 150	50 (>99:<1)

[a] Reaction conditions: **1** (0.25 mmol), **2** (1.0 mmol), **5** (0.75 mmol), $In(OTf)_3$ (63 μmol), 1,4-dioxane (2.0 mL, method A; 0.70 mL, method B). [b] **5a**: 2-methylfuran, **5d**: Me_3SiCN. [c] Isolated yield based on **1**. [d] Determined by GC. [e] Ac = acetyl. [f] Bn = benzyl. [g] The temperature was lowered to 70 °C after the addition of **5a**. [h] The reaction was performed in 1,4-dioxane (0.70 mL) and the temperature was elevated to 100 °C after the addition of **5d**. [i] **5d** (4 equiv.) was used.

toxy or cyano group similarly accepted one molecule of **2a** and of **5a** (Table 2, Entries 3–5). Aryl and heteroaryl acetylenes also participated in the strategy (Table 2, Entries 6 and 7). A bulkier substituent such as –Bn, –*t*Bu, or –Ph on the nitrogen atom of **2** effectively promotes the exclusive formation of **6** (Table 2, Entries 8–10). Me_3SiCN (**5d**) also is available as a nucleophile in the three-component reaction (Table 2, Entry 11).

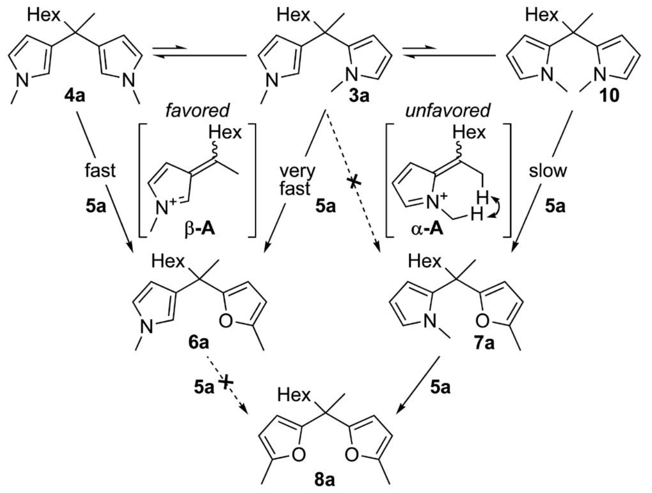
The time course studies on the reaction of DPA **4a**, **3a**, or **10** with **5a** are summarized in Table 3. Both of the reactions of β,β′-DPA **4a** and α,β′-DPA **3a** gave only β-pyrrolyl isomer **6a**, and even α,α′-DPA **10** was transformed into **6a** selectively, along with a small amount of α-isomer **7a** and difuryloctane **8a**. The reactivity order of the three DPAs was found to be **3a** > **4a** > **10**. Scheme 2 illustrates possible routes from the DPAs to the products. In the case of **3a**, cationic species β-**A** and α-**A** are possible intermediates; these result in **6a** and **7a**, respectively. The exclusive formation of **6a** suggests that β-**A** is much more stable than α-**A**, which has serious steric repulsion between the two hydrogen atoms. The reaction of **4a**, which inevitably forms β-**A** upon the elimination of a pyrrolyl group, also gives **6a** exclusively. Considering that the difference between **4a** and **3a** is the leaving group, the fact that the reaction of **3a** is faster than that of **4a** indicates that the α-pyrrolyl group has a superior leaving ability to the β-pyrrolyl group. α,α′-DPA **10**, despite having two α-pyrrolyl groups, was slowly consumed, suggesting that the primary factor contributing to the reactivity of the DPAs is the formation of β-**A** over α-**A** rather than the release of the α-pyrrolyl group over the β-pyrrolyl group. Difuryloctane **8a** was not produced from the reactions of **4a** and **3a**, clearly indicating that **7a** is the only precursor to **8a**.[13] This is most likely a result of the leaving ability of the α-pyrrolyl group being higher than that of the β-pyrrolyl group.

Table 3. Time course studies on reaction of DPAs with 2-methylfuran.



DPA	*t* [min]	Conv. [%] of DPAs (**4a**/**3a**/**10**)[a]	GC yield [%] of **6a** + **7a** (**6a**/**7a**)	GC yield [%] of **8a**
4a	5	52 (92:8:<1)	34 (>99:<1)	<1
	15	88 (90:10:<1)	67 (>99:<1)	<1
	60	98	86 (>99:<1)	<1
3a	5	76 (90:10:<1)	59 (>99:<1)	<1
	15	93 (87:13:<1)	79 (>99:<1)	<1
	40	98	86 (>99:<1)	<1
10	5	20 (<1:<1:>99)	3 (33:67)	<1
	30	49 (2:<1:98)	19 (70:30)	1
	120	82 (9:<1:91)	48 (88:12)	3
	270	95	68 (95:5)	5

[a] The number in parentheses shows the ratio of the remaining DPAs.



Scheme 2. Possible routes from DPAs to products.

Conclusions

We demonstrated the first carbon–carbon bond-forming reaction by the cleavage of the $C(sp^3)$–C(pyrrolyl) bond, where a certain range of carbon nucleophiles are available. The reaction can be performed also as a three-component assembly in an easy manner. The important aspect disclosed herein is the selective formation of intermediary β-**A** from DPAs; this contributes to the high selectivities of β-isomers **6**. Further synthetic applications by utilizing the effect of the β-pyrrolyl group are in progress in our laboratory.

Experimental Section

Synthesis of 6a: Under an argon atmosphere, a mixture of **4a** (35 mg, 0.13 mmol), **5a** (43 mg, 0.52 mmol), and $In(OTf)_3$ (7.3 mg, 13 µmol) in 1,4-dioxane (1.0 mL) was stirred at 85 °C for 1.5 h. To this was added a saturated $NaHCO_3$ aqueous solution (0.5 mL), and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layer was dried with anhydrous Na_2SO_4. Filtration and evaporation of the solvent followed by column chromatography on silica gel (hexane/EtOAc, 50:1) gave **6a** (28 mg, 80% yield; Table 1, Entry 1).

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization data; ^{1}H and ^{13}C NMR spectra for all new compounds.

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[7] The β,β′-adduct (**4a**) is obtained as the major product in the In(OTf)$_3$-catalyzed double addition of *N*-methylpyrrole (**2a**) to 1-octyne (**1a**). See ref.[4] and Supporting Information.

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[10] On treatment of **4a** and **5a** with InCl$_3$ (10 mol-%) under the same conditions, no reaction took place. The high activity of In(OTf)$_3$ is possibly due, at least in part, to its high Lewis acidity induced by the strong electron-withdrawing character of the OTf ligand.

[11] Thienyl(pyrrolyl)alkanes are important units for calixthienopyrroles, as furyl(pyrrolyl)alkanes are for calixfuranopyrroles. See ref.[9]

[12] After consumption of **1a** upon reaction with **2a** was confirmed, **5a** was added to the reaction mixture. Other entries using method A also were carried out in a similar way.

[13] The contamination of α-isomer **7** in several three-component reactions is likely to be related to the increasing content of α,α′-isomers among the remaining DPAs during the reaction (Table 2). For example, before and after the addition of 2-methylfuran (**5a**) in the reaction of Entry 1, the ratio of β,β′-, α,β′-, and α,α′-DPA changed from 86:13:1 to 82:11:7 (10 min later) and then to 78:10:12 (20 min later).

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