Synthesis of pyrroles: reaction of chromium *N*-alkylaminocarbene complexes with α,β-unsaturated aldehydes

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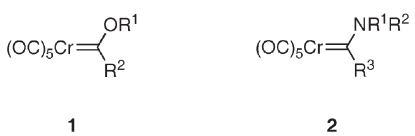
_N_-Alkylaminocarbene complexes of chromium were found to react with α,β-unsaturated aldehydes to give pyrroles in good yields.

Fischer carbene complexes of chromium have long been recognised as useful synthetic intermediates for a wide range of products. Reactions of alkoxy-substituted carbene complexes (**1**, Fig. 1),[1] in particular, have been extensively studied[2] and some of them have been applied to the synthesis of biologically active compounds.[3] In contrast, the chemistry of the corresponding aminocarbene complexes, **2**, is relatively underdeveloped:[4] pioneered by Hegedus, who explored the ketene–chromium chemistry,[2b] several annulation reactions of these aminocarbene complexes with alkynes and/or CO ligands have been reported.[5] Reactions of these carbene complexes with other functionalities such as olefins, however, have been scarcely studied.[6] This fact has diminished the synthetic utility of these complexes for the preparation of nitrogen-containing materials. In this communication, we describe a reaction of *N*-alkylaminocarbene complexes with α,β-unsaturated aldehydes, leading to good yields of substituted pyrroles.[7]

The first examination was performed by means of *N*-isopropylaminocarbene complex **3** and cinnamaldehyde **4a** (Table 1): **3** and **4a** (4 equiv.) were refluxed in toluene for 3 h. The resulting mixture was passed though a small pad of silica gel, and purification by preparative TLC gave *N*-isopropylpyrrole **5a**. But the reactions under these conditions proved to be poorly reproducible (34–86%, Entry 1).

The yield of **5a** was strongly influenced by additives (Entries 2–8); acidic additives such as $BF_3{\cdot}OEt_2$ or AcOH led to deteriorated yields of **5a** (Entries 2, 3). Indeed, when $BF_3{\cdot}OEt_2$ was used, **3** was consumed rapidly. On the contrary, basic additives such as NEt_3 or pyridine gave good yields of **5a** (Entries 4, 5). Use of molecular sieves also increased the yield. Molecular



1 **2**

Fig. 1 Structures of alkoxycarbene complexes (**1**) and aminocarbene complexes (**2**).

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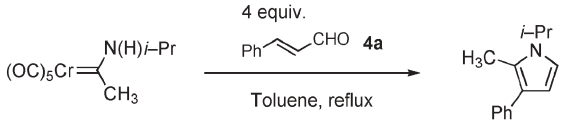
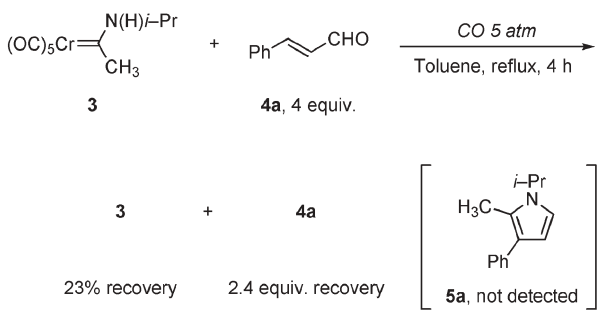
Table 1 Effect of additives



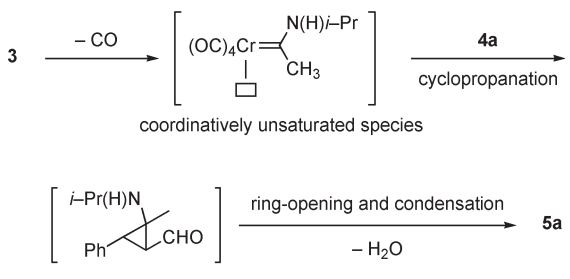
3 **5a**

Entry	Additive (equiv.)	Time/h	**5a** (%)[a]
1	—	2–3	34–86
2	$BF_3{\cdot}OEt_2$ (1.2)	2	—[b]
3	AcOH (1.0)	3	20
4	NEt_3 (1.0)	2	82
5	Pyridine (1.0)	2	81
6	MS 3 Å[c]	3	76
7	MS 4 Å[c]	3	92–94
8	MS 5 Å[c]	3	87

[a] **3** and **4a** were not recovered, unless otherwise stated. [b] **4a** was recovered in 28% yield. [c] 30 mg of molecular sieves was used for 55 mg of **3**.



Scheme 1 Reaction under a CO atmosphere.

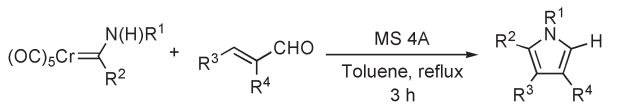


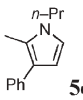
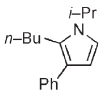
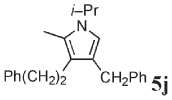
Scheme 2 Possible reaction path.

sieves 4 Å (MS 4 Å) gave the most satisfactory result in terms of the yields and the reproducibility.

This reaction was almost totally inhibited by carbon monoxide (Scheme 1): under 5 atm of CO, **3** and **4a** (4 equiv.) gave 23% and 2.4 equivalent recoveries of **3** and **4a**, respectively. No **5a** was obtained.

Table 2 Formation of pyrroles from aminocarbene complexes and α,β-unsaturated aldehydes[a]



Entry	R^1, R^2	R^3, R^4	Product	**5** (%)
1	*i*-Pr, Me (**3**)	Ph, H (**4a**)	 **5a**	94
2				82[b]
3	*c*-Hex, Me	**4a**	 **5b**	89
4				84[b]
5	*n*-Pr, Me	**4a**	 **5c**	72
6	Allyl, Me	**4a**	 **5d**	70
7	Benzyl, Me	**4a**	 **5e**	74
8				93[b]
9	*i*-Pr, Ph	**4a**	 **5f**	67
10	*i*-Pr, *n*-Bu	**4a**	 **5g**	68
11	**3**	Ph, Me	 **5h**	88 (6 h)
12				63 (6 h)[b]
13	**3**	Me, H	 **5i**	58
14	**3**	3-Phenylpropanal	 **5j**	65

[a] 30 mg of MS 4 Å was used for 55 mg of the complex. [b] The *N*-alkylaminocarbene complex was prepared *in situ* from **1** (R^1 = R^2 = Me) and the corresponding alkylamine (2 equiv., toluene, rt, 5 min).

One possible mechanism for the formation of **5a** is that **3** and **4a** give a cyclopropane intermediate **6** in the reaction medium (Scheme 2).[8] Intermediate **6** undergoes thermal ring-opening[9] and successive condensation gives the product.[10] It is known that cyclopropanation of electron-deficient olefins with chromium carbene complexes proceeds *via* coordinatively unsaturated species.[8a,11] Carbon monoxide pressure might then prevent liberation of the carbonyl ligand and retard the reaction process as described (Scheme 1).[12]

By means of this protocol, various *N*-alkylaminocarbene complexes reacted with α,β-unsaturated aldehydes to give the corresponding pyrroles in good yields (Table 2):[13] not only ordinary alkylaminocarbene complexes (Entries 1, 3, 5) but also allyl- and benzylaminocarbene complexes gave the corresponding pyrroles in good yields (Entries 6, 7). Phenyl- and butyl(isopropylamino)carbene complexes, and aldehydes other than **4a** also worked well to give the corresponding products (Entries 9–11, 13).[14] Interestingly, 3-phenylpropanal could also be employed (Entry 14). In this case, the corresponding α,β-unsaturated aldehyde, generated by condensation *in situ*, gave pyrrole **5j** in 65% yield.

A three-component coupling reaction was also accomplished as an application of this protocol. In the above-mentioned reactions, the starting aminocarbene complexes were prepared from the corresponding methoxycarbene complexes and amines, and purified by column chromatography before use.[15] It would be synthetically useful if the *N*-alkylaminocarbene complexes, generated *in situ*, could be used without purification. Thus we treated methoxycarbene complex **1** (R^1 = R^2 = Me) with 2 equivalents of alkylamine and MS 4 Å in toluene at room temperature for 5 min, and then, 4 equivalents of aldehyde were added. After refluxing the mixture for an additional few hours, we could obtain the desired pyrroles in good yields (Entries 2, 4, 8, 12).

In conclusion, we have found that alkylaminocarbene complexes react with various α,β-unsaturated aldehydes to give pyrroles in good yields. A three-component coupling reaction of alkoxycarbene complexes, amines and aldehydes was also accomplished.

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13 **Typical procedures** (Table 2, Entry 1): to a toluene solution (1 mL) of complex **3** (55.4 mg, 0.200 mmol) were added cinnamaldehyde **4a** (101 μL, 0.801 mmol) and powdered MS 4 Å (29.0 mg) successively. The mixture was refluxed for 3 h and passed though a small pad of silica gel using CH_2Cl_2. The CH_2Cl_2 solution was evaporated under vacuum and the resulting crude mixture was purified by preparative TLC (SiO_2, hexane:AcOEt = 20:1 plus 10% NEt_3) to give 37.5 mg (0.188 mmol) of **5a** in 94% yield. Spectroscopic data for **5a**: ^{1}H NMR (δ, $CDCl_3$, 400 MHz) 1.45 (6H, d, J = 6.8 Hz), 2.35 (3H, s), 4.35 (1H, septet, J = 6.8 Hz), 6.28 (1H, d, J = 3.0 Hz), 6.74 (1H, d, J = 3.0 Hz), 7.18 (1H, tt, J = 7.0, 1.6 Hz), 7.33–7.41 (4H, m); ^{13}C NMR (δ, $CDCl_3$, 100 MHz) 10.7, 23.5, 47.0, 107.5, 114.8, 121.7, 124.2, 124.9, 128.2 (the signal intensity and C–H COSY experiment suggested that signals of *ortho* and *meta* carbons of the phenyl group overlap at 128.2 ppm), 137.6; IR ($\tilde{\nu}$, $CHCl_3$) 1236, 1342, 1499, 1603, 2982 cm^{-1}; E. A. Found. C 84.40%, H 8.50%, N 7.26%; calcd. for $C_{14}H_{17}N$, C 84.37%, H 8.60%, N 7.03%.

14 When **3** and methacrolein were refluxed in toluene for 1 h, **3** was consumed completely but only a trace amount of the corresponding pyrrole was obtained. Polymerisation of the aldehyde probably took place.

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