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Transition Metal Catalysed Alkylation of Pyridines and Indoles

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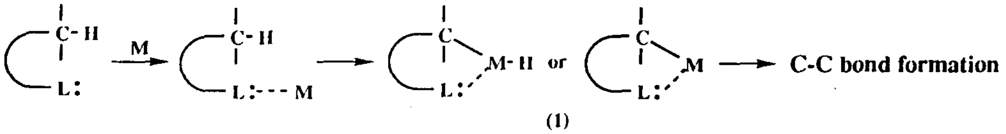
Abstract: Heating 3- or 4-acetyl pyridine with alkenes in toluene in the presence of 5-10mol% of $RuH_2CO(PPh_3)_3$ afforded the mono- or a mixture of mono- and di-alkylated products in good yield. Alkylation of acetylindole derivatives was also achieved with similar efficiency.

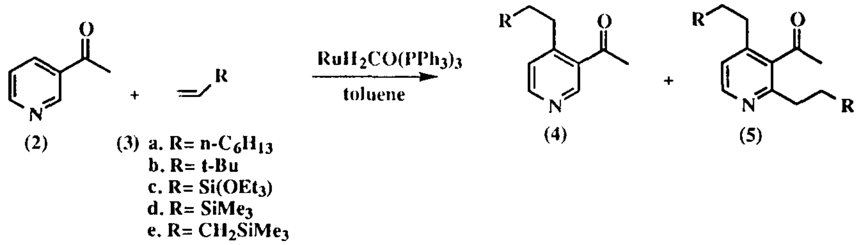
Reactions of transition metal complexes in which an organic ligand undergoes intramolecular metallation with formation of metal-carbon σ-bond to form (**1**) (**Scheme 1**) are known as a cyclometallation reactions.[1] These reactions, discovered over thirty years ago,[2] have been intensively investigated in the last three decades. Much work on the preparation and characterisation of the cyclometallated complexes of type (**1**) has been published[3] and the high level of interest reflects the potential synthetic applicability of cyclometallated complexes.[4] Various interesting catalytic reactions have been reported which from the point of view of synthetic organic chemistry have limited applicability.[5] Recently, more robust processes have been discovered which employ ruthenium[6] and rhodium[7] catalysed cascade cyclometallation-C - C bond formation (**Scheme 1**, M= Ru, Rh). As a part of our ongoing interest[8] in transition metal catalysed Friedel-Crafts type reactions, we were interested in applying this new methodology to the alkylation of heterocyclic compounds.



(1)

Scheme 1

Initial work was centred on the alkylation of the pyridine ring. It was expected that transition metal catalysed alkylation would give some advantages over the existing methods that normally require strong nucleophiles, such as RMgX or RLi, or produce a mixture of products.[9] The results are shown in **Scheme 2** and **Table 1**. Heating 3-acetyl pyridine and excess of an alkene in toluene in the presence of $RuH_2CO(PPh_3)_3$ (5mol%) produced the expected product in moderate to good yield. The use of 1-octene (**Table 1**, entry 1) did not prove to be efficient due to competitive double bond isomerisation in the presence of catalyst, forming less reactive internal alkenes. Alkene isomerisation can be avoided by using alkenes without an α - C-H bond, as demonstrated by the case of 3,3-dimethylbutane (**Table 1**, entry 2). Silicon substituted alkenes, as already demonstrated,[6] proved to be much more efficient producing a mixture of mono (**4**)- and di-alkylated (**5**) products (**Table 1**, entries 3 and 4) regioselectively and in good yield . The monoalkylated product at the 2-position of the pyridine ring was not observed showing that dialkylated product (**5**) was formed by further alkylation of (**4**) and indicating higher reactivity of the 4-H.



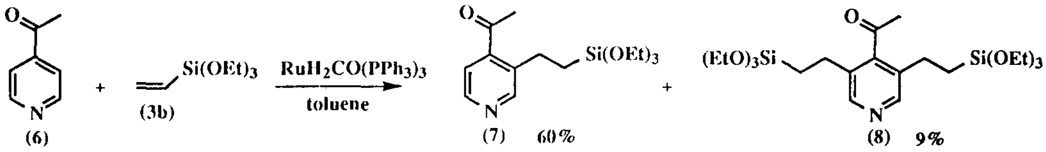
Scheme 2

Table 1[a]

entry	*alkene*	(2) : (3)	*yield (%)*[b] (4)	*yield (%)*[b] (5)
1	(3a)	1 : 4	11	-
2	(3b)	1 : 4	50(>80)[c]	-
3	(3c)	1 : 3	56	7
4	(3d)	1 : 3	45	31
5	(3e)	1 : 3	40(>80)[c]	-

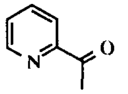
[a] 5mol% of the catalyst, reaction time 24-40h, [b] isolated yields, [c] yield based on recovered starting material

Similarly, 4-acetyl pyridine (**6**) under the same conditions but with 10mol% of the catalyst afforded mixture of mono (**7**)- and di-alkylated (**8**) products in 60 and 9% yield respectively (**Scheme 3**).

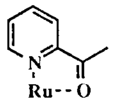


Scheme 3

Attempts to use 2-acetyl pyridine as a substrate and (3c) as an alkylating reagent in this reaction failed probably due to (**9**) acting as bidentate ligand forming (**10**) and so preventing insertion of the metal into the α C-H bond and further reaction with an alkene.

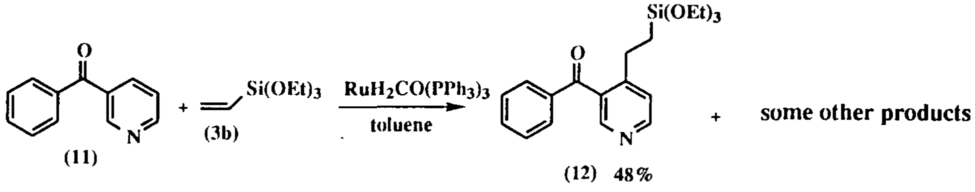


(9)



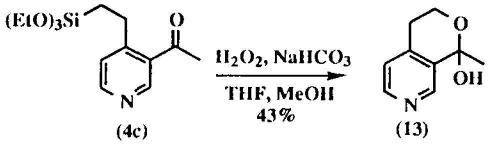
(10)

We also briefly investigated the regioselectivety of the Ru-catalysed alkylation of 3-benzoylpyridine (**11**). The reaction of (**11**) and (**3b**) (1.1 equivalent) in boiling toluene in the presence of 10mol% of the catalyst afforded (**12**) in 48% yield accompanied by an inseparable mixture of di- and tri-alkylated products (NMR and mass spectra). These results indicate higher reactivity of the more electron deficient pyridine C-H bond.



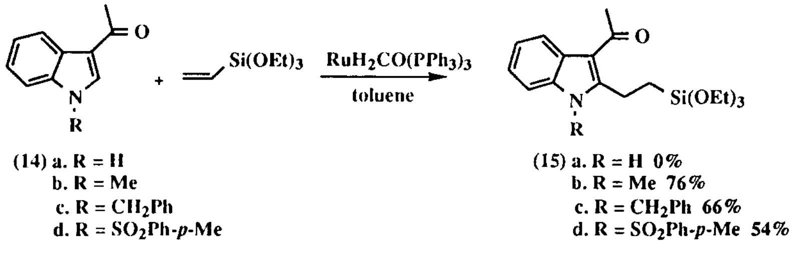
Scheme 4

It was also demonstrated that $(EtO)_3Si$ substituent in (**4c**) could be oxidatively removed using standard conditions[10] to afforded (**13**) in 43% yield (**Scheme 5**).



Scheme 5

Similar efficiency was also observed in alkylation of the indole ring (**Scheme 6**). The only requirement was the presence of an N-protecting group since the free N-H deactivated the catalyst. All reactions were performed under similar conditions with 10mol% of $RuH_2CO(PPh_3)_3$ affording products (**15b-d**) in good yield. The reaction was shown to be regiospecific producing only the product of the alkylation of the pyrrole ring. This can be explained in terms of formation of the more favoured five-membered transition state[3] involving insertion of the metal into the pyrrole C-H bond, as opposed to the six-membered transition state if the benzene C-H bond is cleaved in the reaction. Murai et al. have been reported similar alkylation of 2-acetyl derivatives of thiophene, furan and pyrrole and also an example of regiospecific alkylation of 3-acetylthiophene.[6, 11]



Scheme 6

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References:

1. Bruce, M.I.; *Angew.Chem.Int.Ed.*,1977, *16*, 73-86; Ryabov, A.D.; *Chem.Rev.*, **1990**, *90*, 403-424.

2. Chatt, J.; Davidson, J.M.; *J.Chem.Soc.*, **1965**, 843-855; La Placa, S.J.; Ibers, J.A.; *Inorg. Chem.*, **1965**, *4*, 778-783.
3. Omae, I.; *Chem.Rev.*, **1979**, *79*, 287-321; Omae, I.; *Coord.Chem.Rev.*, **1982**, *42*, 245-257; Omae, I.; *Coord.Chem.Rev.*, **1980**, *32*, 235-271.
4. Ryabov, A.D.; *Synthesis*, **1985**, 233-252.
5. Jordan, F.R.; Taylor, D.F.; *J.Am.Chem.Soc.*, **1989**, *111*, 778-779; Moore, E.J.; Pretzer, W.R.; O'Connell, J.T.; Harris, J; Labounty, L.; Chou, L.; Grimmer, S.S; *J.Am.Chem.Soc.*, **1992**, *114*, 5888-5890; Hsu, G.C.; Kosar, W.P.; Jones, W.D.; *Organometallics*, **1994**, *13*, 385-396.
6. Murai, S.; Chatani, N.; Kakiuchi, F.; *Catalysis Surveys Jpn.*, **1997**, *1*, 35-51 and references cited therein; Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S.; *J.Org.Chem.*, **1997**, *62*, 2604-2610.
7. Lim, Y.G.; Kang, J.B.; Kim, Y.H.; *J.Chem.Soc.Perkin 1*, **1996**, 2201-2206.
8. Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V.; *Tetrahedron Lett.*, **1995**, *36*, 8137-8140.
9. Smith, D.M.; in *Comprehensive Organic Chemistry*, ed. Sammes, P.G.; Pergamon Press, **1979**, vol 4, p.3-84.
10. Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M.; *Organometallics*, **1983**, 2, 1694-1696.
11. Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S.; *Bull.Chem. Soc.Jpn.*, **1995**, *68*, 62-83.

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