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# A New Ruthenium Catalysed Reaction: the Benzylation of Aromatic Heterocyclic Compounds

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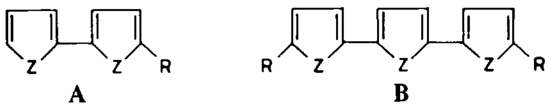
The Friedel–Crafts reaction represents a considerable potential in organic synthesis and has largely been used and developed in the benzylation process of aromatic hydrocarbons [1]. The direct benzylation of aromatic heterocycles is disfavored and few efficient examples have been described [2]. Recently, we reported a new alkylation reaction of heterocyclic compounds, promoted by ruthenium catalysts in alcohol, which involved carbon–carbon bond formation giving rise to products of type **A** and **B** [3] (Scheme 1). When the alcohol was replaced by benzylbromide or benzylchloride, the ruthenium complexes behaved as benzylation catalysts of aromatic heterocycles. This preliminary communication describes the first examples of ruthenium catalysed benzylation of thiophene, furan, thianaphthalene and benzofuran.



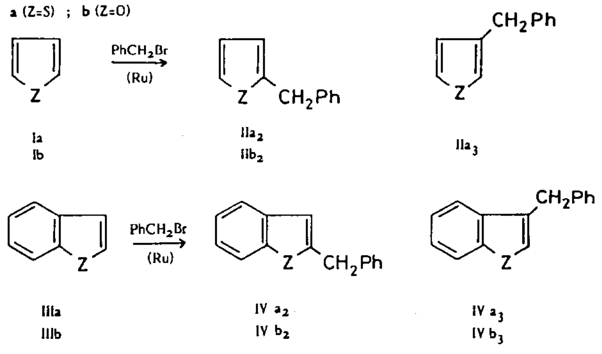
Scheme 1.

The standard procedure is as follows: thiophene (21 mmol), benzylbromide (29.6 mmol), pentane (10 ml) and $RuCl_3 \cdot xH_2O$ (1 mmol) are combined in a 300 ml stainless steel autoclave and maintained at 140 °C for 24 h, whilst stirring under nitrogen. The reaction mixture, analysed by gas chromatography, showed the formation of 2-benzyl and 3-benzylthiophene (**IIa$_2$** and **IIa$_3$**) (18–20%) and as a by-product dibenzyl (7%), (Table I, Scheme 2). In a similar way, furan (**Ib**), thianaphthalene (**IIIa**) and benzofuran (**IIIb**) were reacted with benzylbromide and the corresponding benzylated derivatives were obtained **IIb$_2$** (13.5%), **IVa$_2$/a$_3$** (42%), **IVb$_2$/b$_3$** (41%) (Table II)[†].

TABLE I. Influence of Catalysts and Solvents on the Benzylation of Thiophene Ia

| Catalysts | Solvent | Yields of benzylated products **IIa**$^{a,b}$ |
|---|---|---|
| $RuCl_3 \cdot xH_2O$ | THF | 20 |
| $(pcy)RuCl_2PMe_3$ $^c$ | THF | 18 |
| $(NBD)RuCl_2(Py)_2$ $^d$ | THF | 18.4 |
| $((pcy)RuCl_2)_2$ $^c$ | THF | 14.5 |
| $Ru_3(CO)_{12}$ | THF | 3 |
| $RuCl_3 \cdot xH_2O$ | $CH_3CN$ | 16.5 |
| $RuCl_3 \cdot xH_2O$ | pentane | 41.5(31.5)$^b$ |
| $RuCl_3 \cdot xH_2O$ | neat | 30(24)$^b$ |

$^a$Percent yields, based on thiophene, determined by gas chromatography analysis using an internal standard, isomers ratio $IIa_2/IIa_3$ in all examples = 91/9. $^b$Yields, in brackets, of isolated product. $^c$(pcy) = *para*-cymene. $^d$NBD = norbornadiene, Py = pyridine.



Scheme 2.

A range of ruthenium complexes, e.g. $(pcy)RuCl_2PMe_3$, $(NBD)RuCl_2(Py)_2$, $((pcy)RuCl_2)_2$ and $Ru_3(CO)_{12}$ have also been found to act as catalysts for the benzylation process. There proved to be a greater efficiency in reactions using an aprotic solvent (pentane) rather than a polar solvent (THF, $CH_3CN$). It is also apparent that, without solvent, the ruthenium complexes are able to catalyse the reaction (Table I).

The influence of the nature of the benzylation reagent has been studied. Our results (Table III) show that the presence of an electron-withdrawing (Br) or electron-donating ($CH_3$) group on the phenyl ring has no significant effect. The conversion of thiophene into benzylated products varied in the range of 25%–33%. Consequently, this reaction can be used for a wide variety of substituted benzylhalides.

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[†] The benzylated products were extracted by distillation and purified over alumine (eluent: ether–pentane). IR, $^1$H and $^{13}$C NMR data of the isolated compounds were consistent with the assigned structure. All compounds have yielded satisfactory high resolution mass spectra.

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TABLE II. Benzylation of Heterocyclic Compounds

| Substrate | Catalyst | Solvent | Yield of benzylated product$^{a,b}$ | | |
|---|---|---|---|---|---|
| Furan | $RuCl_3 \cdot xH_2O$ | THF | **IIb$_2$** | 6 | |
| | $(pcy)RuCl_2PMe_3$$^{c}$ | THF | | 8.6 | |
| | $RuCl_3 \cdot xH_2O$ | neat | | 13.5 | |
| Thianaphthalene | $RuCl_3 \cdot xH_2O$ | pentane | **IVa$_2$, a$_3$** | 42 | (82/18) |
| | $RuCl_3 \cdot xH_2O$ | neat | | 45 | (80/20) |
| | $((pcy)RuCl_2)_2$$^{c}$ | THF | | 29 | (85/15) |
| Benzofuran | $RuCl_3 \cdot xH_2O$ | THF | **IVb$_2$, b$_3$** | 28 | (73/27) |
| | $((pcy)RuCl_2)_2$$^{c}$ | THF | | 19 | (89/11) |
| | $RuCl_3 \cdot xH_2O$ | pentane | | 41 | (80/20) |
| | $RuCl_3 \cdot H_2O$ | neat | | 40 | (85/15) |

[a] Percent yields based on heterocyclic compound, determined by gas chromatography using an internal standard. [b] In brackets, isomers ratio of 2- and 3-benzylated products respectively. [c] (pcy) = *para*-cymene.

TABLE III. Influence of the Benzylation Reagent on the Reaction with Thiophene[a]

| Benzylation agent | Yield IIa$_2$/IIa$_3$ |
|---|---|
| *p*-$CH_3C_6H_4CH_2Br$ | 35 (65/35) |
| *o*-$CH_3C_6H_4CH_2Br$ | 25 (85/15) |
| *p*-$BrC_6H_4CH_2Br$ | 31.5 (58/42) |
| *o*-$BrC_6H_4CH_2Br$ | 26.2 (60/40) |

[a] Catalyst: $RuCl_3 \cdot xH_2O$ without solvent.

Although the mechanism of the benzylation reaction is not clear, the formation of dibenzyl as a by-product suggests that the coupling of two benzyl radicals occurred. The involvement of a radical intermediate in the catalysed benzylation reaction is supported by (i) the free radical behaviour observed in reactions of ruthenium complexes with alkyl halides [4] and (ii) the fact that homolytic phenylation of thiophene gives the same ratio of 2- and 3-phenylthiophene [5].

The above results show strong differences in the behaviour, toward catalytic benzylation, of the heterocycles **I** and **III**. The negligible reactivity of the 3-position of furan [6] explains the absence of the corresponding benzylated product. Benzofuran and thianaphthalene behave similarly toward 2- and 3-substitution [7, 8] and lead to the better yields of benzylated products.

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