Pergamon

Tetrahedron Letters, Vol. 38, No. 37, pp. 6493-6496, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01512-8

Organometallic-type Reactions in Aqueous Media Mediated by Indium. Allylation of Acyloyl-imidazoles and pyrazoles. Regioselective Synthesis of β,γ-Unsaturated Ketones.

Vernal J. Bryan, Tak-Hang Chan*

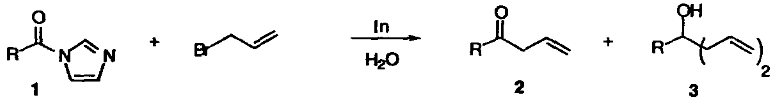
Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

Abstract: *Indium mediated coupling of allylic bromide with acyloyl-imidazoles or pyrazoles in aqueous media gives the corresponding tertiary alcohols or ketones in good yield. The reaction provides a facile regioselective synthesis of β,γ-unsaturated ketones and its usefulness is demonstrated by the synthesis of the monoterpene artemesia ketone.*

Recently, organometallic-type reactions in aqueous media have attracted considerable interest for the formation of carbon-carbon bonds in numerous organic synthesis[1]. In particular, the indium mediated allylation of carbonyl compounds in aqueous media to give the corresponding homoallylic alcohols has been found to be especially useful.[2] The reaction has been used to allylate a wide variety of aldehydes and ketones,[3] in both an inter- and intra-molecular fashion.[4] It has furnished various structural types and has been used most conveniently, for the synthesis of carbohydrates.[5] Of considerable significance is the fact that the reaction can be regio- as well as stereoselective.[6] The coupling of γ-substituted allylic halides with prochiral aldehydes, for example, produces predominantly the *anti* diastereomers.

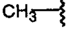
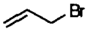
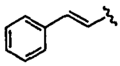
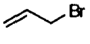
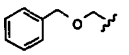
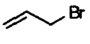
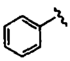
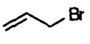
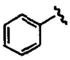
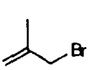
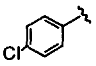
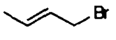
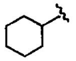
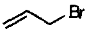
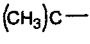
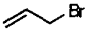
So far, the carbonyl component in the indium mediated coupling reaction in aqueous media has been confined to aldehydes and ketones. Carboxylate esters and even carboxylic acids show remarkable stability towards the reaction conditions. This is in stark contrast to the reactivity of ester or acid functions to conventional organometallic reagents in organic solvents. We are therefore interested in exploring the reactivity of various activated carboxylates under the indium mediated conditions in water to broaden the scope of the reaction.[7] We report here the extension of the indium mediated reaction to include the allylation of various carboxylic acid derivatives in aqueous media. Specifically we have found that indium mediates the allylation of acyloyl-imidazoles (1) in a rapid manner, producing a mixture of the corresponding homoallyic ketones (2) and symmetrical tertiary alcohols (3) according to the following scheme in good yields (Table 1).

Scheme 1.



It is clear from the results in Table 1 that simple aliphatic and aryl acyloyl-imidazoles (entries 1-5) react with allyl bromide and indium in aqueous media to give predominantly the corresponding tertiary alcohol **3** with only a trace of the intermediate ketone **2**. Efforts to increase the yield of **2** by varying the order of addition of reagents or the proportions of **1** with respect to either the allyl bromide or indium were not successful. This suggests that the intermediate ketone **2** reacts faster with allyl bromide/indium in aqueous medium than **1** itself. It is only when the steric size of the R group increases (entries 6 and 7), then the yield of the ketone **2** increases as well. In the case of pivaloyl-imidazole (entry 7), the corresponding ketone could be obtained almost exclusively.

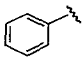
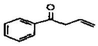
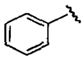
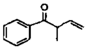
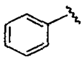
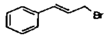
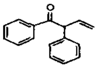
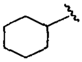
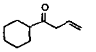
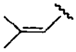
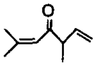
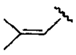
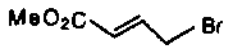
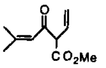
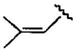
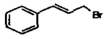
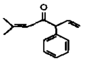
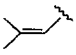
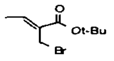
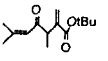
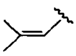
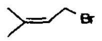
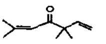
Table 1: Allylation of Acyloyl-imidazoles[a]

Entry	R	Bromide	% Yield	% Ketone	% 3° Alc
1			>80	0	100
2			88	0	100
3			90	0	100
4			95	6	94
5			95	5	95
6			90	50	50
7			86	33	67
8			85	93	7

[a] Acyloyl-imidazoles :Bromide:Indium (1.5:1:3); Stirred at 0°C (Sonication used if stirring proved difficult); Monitored by tlc; Ratios determined using ^{1}H NMR of the crude.

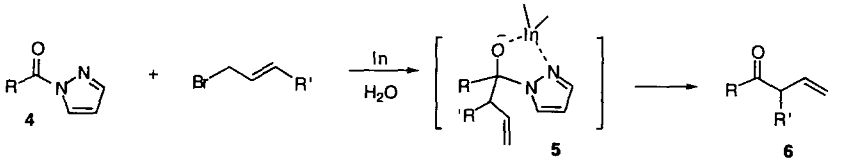
The ketone compound **2** can be obtained in high yield, however, if acyloyl-pyrazole (**4**) is used in place of the acyloyl-imidazole in the reaction. Thus, benzoyl-pyrazole (**4**, R=Ph) reacted with allyl bromide and indium in water under identical conditions to give predominantly the homoallylic ketone **2** (R=Ph). We attribute this selectivity to the chelating ability of the second nitrogen of the pyrazole ring to stabilize the intermediate **5**, thus allowing for the completion of the reaction of **4** with allylindium before the formation of the ketone **2**. Even more interestingly, when substituted allylbromide was used, ketone formation was favored with high regioselectivity, leading to the corresponding α-substituted-β,γ-unsaturated ketone **6**. Thus, for example, cinnamyl bromide was coupled to benzoyl-pyrazole to give in nearly quantitative yield one regioisomeric ketone (entry 3, Table 2).

Table 2: Allylation of Acyloyl-pyrazoles[a]

Entry	R	Bromide	% Yield	Major Product	% Ketone	% 3° Alc
1[b]			90		75	25
2			88		100	0
3			95		100	0
4[b]			90		>95	<5
5			92		95	5
6[c]			50		100	0
7			92		100	0
8[d]			75		100	0
9			65		100	0

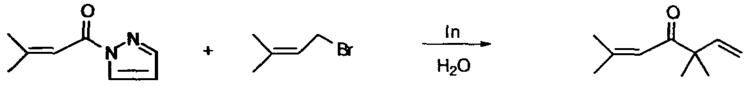
[a] All reactions were performed at 0°C on a mmol scale using 2ml of H_2O and 3mmols of indium. Reactions were monitored by tlc and ratios were determined using ^1H NMR of the crude. Purification was performed using chromatography over silica gel with 99:1(hexane : ethyl acetate) as eluent. [b](1.5 : 1)(acyloyl-pyrazole : bromide) was used; [c](1 : 2)(acyloyl-pyrazole : bromide) was used. [d]Reaction was performed at room temperature for more than 12hrs.

Scheme 2.



We have demonstrated the synthetic usefulness of this reaction by a facile synthesis of the artemesia ketone 7 which is a monoterpene isolated from the volatile oil of *Santolina chamaecyparissus* L. and *Artemisia annua* L.[8] Coupling of dimethylacryloylpyrazole with dimethylallyl bromide in water with indium gave the ketone 7 regioselectively in 65% isolated yield.[9]

Scheme 3.



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Acknowledgement: We thank NSERC and FCAR for financial support of this research.

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1. (a) Chan, T. H.; Li, C. J.; Wei, J. Y.; Lee, M. C., *Can. J. Chem.*, **1994**, *72*, 1181; (b) Li, C. J., *Chem. Rev.*, **1993**, *93*, 2023; (c) Chan, T. H.; Isaac, M. B., *Pure & Appl. Chem.*, **1996**, *68*, 919.
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(*Received in USA* 16 *June* 1997; *accepted* 11 *July* 1997)