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Indium(I) bromide-promoted stereoselective preparation of (*E*)-α,β-unsaturated ketones via sequential intermolecular aldol-type coupling/elimination reactions of α,α-dichloroketones with aldehydes

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Abstract

Indium(I) bromide promotes the reaction of α,α-dichloroketones with aldehydes to produce (*E*)-α,β-unsaturated ketones, exclusively. The transformation occurs via two sequential reactions, an aldol-type coupling between the two carbonylic reagents followed by an elimination process.

Keywords: Indium; Organoindium; Carbon–carbon bond formation; Aldol-type coupling; Elimination reaction; Sequential chemical reactions

1. Introduction

Aldol coupling between carbonyl compounds followed by elimination and the Wittig reactions are amongst the most important methods to prepare α,β-unsaturated carbonyl compounds [1]. However, both methods suffer of undesired limitations. Self condensation products are frequently encountered as by-products in the former process, when both carbonyl starting materials are enolizable substances. Similarly, in the Wittig reactions, the phosphoranes and the strong bases used to generate them are not compatible with enolizable carbonyl compounds and again can lead to self condensation products. Recent work has demonstrated that α,α-dihalogenocarbonyl compounds can be reduced by samarium(II) iodide or chromium(II) chloride; the products from these reductions couple with aldehydes to produce, after elimination, α,β-unsaturated carbonyl compounds [2]. The rigorous stereoselectivity of the reaction leading exclusively to the (*E*)-isomers was considered an important improvement over the previous mentioned methods.

Recently, we have demonstrated that dibromoacetonitrile reacts with aldehydes mediated by indium monobromide to afford 2-alkenenitriles, through a sequence of a coupling followed by an elimination process [3]. In this paper, we aim to show that indium monobromide is also an effective reagent to promote the reaction between α,α-dichloroketones **1** with aldehydes to produce certain (*E*)-α,β-unsaturated ketones **2** (Scheme 1) via the same coupling/elimination sequence.

2. Results and discussion

The reaction between equimolar amounts of α,α-dichloroketones **1** and selected aldehydes promoted by 2 M equiv. of InBr, in refluxing THF, gives rise to the (*E*)-α,β-unsaturated ketones **2** products described at Table 1.

The stereochemistry of the olefinic products **2a**–**k** was determined by ^{1}H NMR spectroscopy; the coupling constants relating the two olefinic protons in the range 15.7 ± 0.6 Hz (see Section 4) characterize the exclusive production of the *E*-isomers.

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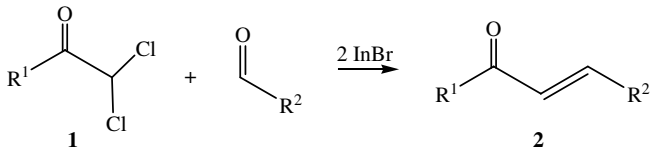


Scheme 1. InBr-promoted synthesis of (*E*)-α,β-unsaturated ketones **2**.

Table 1
The generality of the InBr-promoted synthesis of (*E*)-α,β-unsaturated ketones **2**

Entry	R^1	R^2	Yield
a	C_6H_5	C_6H_5	77
b	C_6H_5	*p*-ClC_6H_4	78
c	C_6H_5	*p*-BrC_6H_4	66
d	C_6H_5	*o*-BrC_6H_4	64
e	C_6H_5	*p*-$CH_3C_6H_4$	56
f	C_6H_5	*p*-$CH_3OC_6H_4$	55
g	C_6H_5	*n*-C_3H_7	60
h	C_6H_5	*i*-C_3H_7	57
i	C_6H_5	*n*-C_9H_{19}	62
j	CH_3	*p*-ClC_6H_4	33
k	CH_3	*p*-$CH_3OC_6H_4$	32
l	CH_3	*n*-C_9H_{19}	Traces

The proposed mechanism for this transformation consists of two sequential reactions and it is given at Scheme 2. The first reaction is an aldol coupling between the aldehyde with the indium(III) enolate **3**, generated by the oxidative insertion of InBr into one of the carbon–chlorine bonds of the α,α-dichloroketone **1**, as we have determined previously when, after aqueous work-up, we have isolated the 2-chloro-3-hydroxy-propan-1-one derivatives **6** as a mixture of diastereoisomers [4a]. A second oxidative insertion of the monobromide into the carbon–chlorine bond of the indium alkoxide **4** produces the dimetallic intermediate **5**, which is the key species leading to the enones **2**, through an elimination process.

The rigorous stereoselectivity during elimination of the indium(III) oxide $(X_2In)_2O$ from intermediate **5** is understood in terms of the chairlyke six-membered transition state depicted at Fig. 1, in which the aldehyde R^2 group adopts equatorial orientation in relation to the dichloroketone R^1 substituent to avoid 1,3-diaxial repulsive interac-

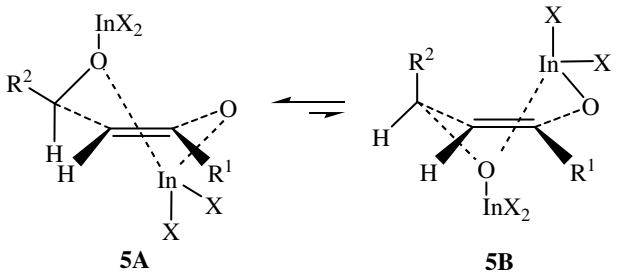
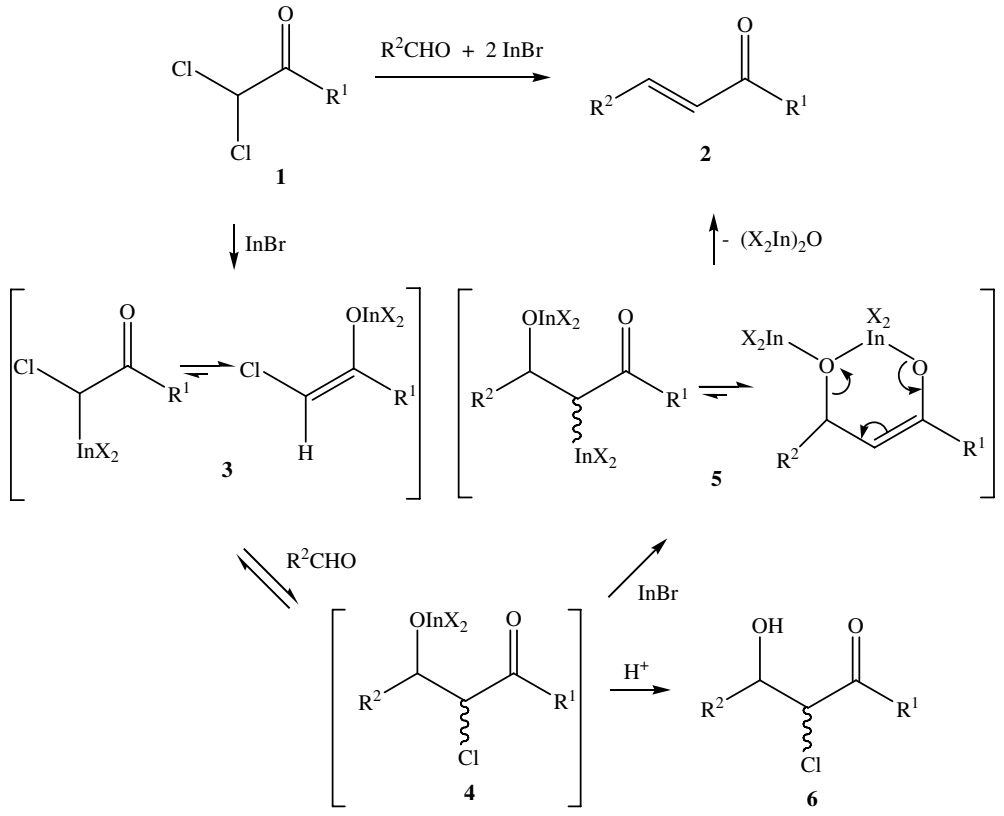


Fig. 1. Transition state model.



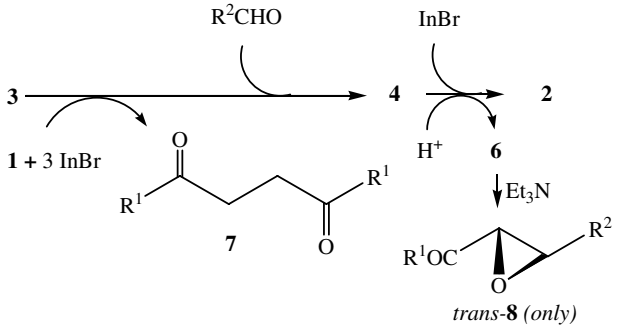
Scheme 2. Proposed mechanism for InBr-mediated synthesis of (*E*)-α,β-unsaturated ketones **2**.

tion. Such an intermediate was proposed previously by Concellón and co-workers when studying similar processes promoted by SmI_2 or $CrCl_2$ and seems very appropriated to explain the present InBr-mediated process [2]. A comparison between the stereoselective aspects of this sequence of reactions involving dichloroketones and aldehydes with the analogous process with dibromoacetonitrile previously reported is important because it lends some indirect support to the proposed cyclic intermediate **5**. No cyclic intermediate is possible from the nitrile due to the linear geometry of its CN bond. Therefore, as expected, dibromoacetonitrile affords mixtures of both (*Z* and *E*) diasteroisomers of the corresponding 3-organyl-2-alkenenitriles.

The efficiency of the reaction is governed by the nature of both organyl groups, R^1 and R^2. The chalcones **2a–f** and the 3-alkyl-1-phenyl-prop-2-en-1-one derivatives **2g–i** derived from α,α-dichloroacetophenone were obtained in moderate to good yields. On the other hand, the products derived of α,α-dichloroacetone were obtained in low yields, and only from reactions with aromatic aldehydes (**2j–k**). At this point, it is important to notice that the major by-products which were isolated from ineffective reactions were the aldehyde starting material and the corresponding α-chloroketone; the dynamic equilibrium involving the proposed intermediates **3** ⇌ **4**, which was discussed in our previous work [4a], is an important operative feature in the proposed sequence of reactions and accounts for the observed by-products. Successful reactions (entries **a–i**) seem to be closely associated with the thermodynamic stability of the enone product **2** and are achieved preferentially for 1-aryl and 3-aryl substituted products. Comparison of the results obtained from this InBr-mediated process with the two other sequential methods to transform α,α-dichloroketones and aldehydes into α,β-unsaturated ketones **2** promoted by SmI_2 and $CrCl_2$ [2c] is important to guide to the correct choice amongst these reagents. The reaction is quite general when promoted by a sixfold excess of $CrCl_2$, while certain aldehydes resisted the transformation promoted by SmI_2. The present InBr-promoted method does not require excess of the inorganic reagent and shows generality similar to the process promoted by $CrCl_2$, although smaller yields were systematically obtained.

3. Conclusion

We have demonstrated how to use indium monohalides to produce reactive organoindium(III) species from *gem*-dihalogenoketones, capable of useful organic transformations [3,4a]. The indium enolate, **3** obtained from the oxidative insertion of InBr into one of the carbon–chlorine bonds of the dichloroketone can be used for several purposes: it couples with a second molecule of the dichloroketone to produce, after reduction with excess of indium monobromide, the corresponding 1,4-butanediones, **7** [5]; alternatively, the enolate condensates with an aldehyde to give the corresponding 2-chloro-3-hydroxy-propan-1-one derivative, **6** [4a]; which can easily be converted into the *trans*-epoxyde **8** by treatment with a convenient base (Scheme 3) [4a].



Scheme 3. Products derived from indium enolate **3**.

Now, we have extended this sequence of reactions to produce the (*E*)-α,β-unsaturated ketones **2**, through an aldol coupling followed by an elimination reaction. The key step in the sequence is the ejection of the β-related chlorine and oxygen atoms of the diindium intermediate **5**. The sequential reactions are conducted in neutral conditions and offer a single step, one-pot, new protocol for preparing enones **2**. Despite the fact that the primary enolate **3** is produced as a mixture of diastereoisomers [4a], the *E*-isomers of the enones **2** were obtained with complete stereoselectivity, through a transition state **5** that minimize steric repulsion between the organyl groups attached to the aldehyde and to the dichloroketone starting materials. Moreover, we expect that this work shed some light on how to use indium(I) salts to prepare reactive organoindium(III) compounds capable of useful organic transformations.

4. Experimental section

4.1. General data

Indium monobromide was prepared by heating indium metal and indium tribromide (molar ratio 2:1) in a vacuum sealed tube, at 450 °C for 24 h. α,α-Dichloroacetone and α,α-dichloroacetophenone (Aldrich) were distilled before used under atmospheric and reduced pressures, respectively. All the aldehydes were obtained from commercial suppliers and purified, when necessary, according to standard procedures [6]. ^1H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^1H at 200.13 MHz and ^{13}C at 50.32 MHz). Mass spectra were registered in a HP 6890 GC (equipped with a split–splitless injector and a cross-linked HP-5 capillary column measuring of 30 m and with internal diameter of 0.32 mm) connected to a HP 5973 MSD spectrometer, with helium as the carrier gas.

4.2. Indium(I) bromide-promoted stereoselective preparation of (E)-α,β-unsaturated ketones via sequential intermolecular aldol-type coupling/elimination reactions of α,α-dichloroketones and aldehydes. General experimental procedure

A Schlenk test tube equipped with a condenser, truly dried under high vacuum, was charged with 2 mL of dry (sodium) THF, 195 mg (1.0 mmol) of the red solid InBr and the α,α-dichloroketones (0.5 mmol). To this mixture was added 0.5 mmol of the aldehyde and the reaction was kept under reflux for l4 h. At the end of this period, the reaction was quenched with water. The organics were extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated to dryness. The (*E*)-α,β-unsaturated ketones **2** were separated by column chromatography with hexanes or hexanes–ethyl acetate mixtures. Yields of reactions are given in Table 1, and spectroscopic data for products **2a**–**l** are as follow:

(*E*)-1,3-Diphenyl-2-propen-1-one, **2a** (CAS: 614-47-1) [7]: ^{1}H NMR ($CDCl_3$): $\delta = 7.39$–7.67 (m, 8H), 7.54 (d, $J = 15.7$ Hz, 1H), 7.83 (d, $J = 15.7$ Hz, 1H), 8.01–8.06 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 121.82$, 128.28, 128.32, 128.44, 128.77, 130.37, 132.62, 134.65, 137.97, 144.60, 190.24; MS (EI, 70 eV): *m*/*z* (%) = 208 (100) [M], 131 (76), 103 (76), 77 (100), 51 (69).

(*E*)-3-(4-Chlorophenyl)-1-phenyl-2-propen-1-one, **2b** (CAS: 956-04-7) [8]: ^{1}H NMR ($CDCl_3$): $\delta = 7.39$ (d, $J = 8.0$ Hz, 2H), 7.51 (d, $J = 15.6$ Hz, 1H), 7.49–7.62 (m, 5H), 7.76 (d, $J = 15.6$ Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 122.42$, 128.47, 128.65, 129.22, 129.56, 132.91, 133.34, 136.40, 137.98, 143.29, 190.22; MS (EI, 70 eV, for ^{35}Cl): *m*/*z* (%) = 242 (79) [M], 207 (50), 165 (41), 105 (53), 77 (100).

(*E*)-3-(4-Bromophenyl)-1-phenyl-2-propen-1-one, **2c** [9]: ^{1}H NMR ($CDCl_3$): $\delta = 7.44$ (d, $J = 15.7$ Hz, 1H), 7.38–7.55 (m, 7H), 7.67 (d, $J = 15.7$ Hz, 1H), 7.91–7.96 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 122.63$, 124.77, 128.47, 128.65, 129.75, 132.20, 132.90, 133.84, 138.04, 143.32, 190.20; MS (EI, 70 eV, for ^{79}Br): *m*/*z* (%) = 286 (38) [M], 207 (57), 105 (57), 77 (100).

(*E*)-3-(2-Bromophenyl)-1-phenyl-2-propen-1-one, **2d**: ^{1}H NMR ($CDCl_3$): $\delta = 7.13$–7.30 (m, 2H), 7.35 (d, $J = 15.7$ Hz, 1H), 7.40–7.68 (m, 5H), 7.92–7.97 (m, 2H), 8.06 (d, $J = 15.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 125.00$, 125.84, 127.67, 127.83, 128.60, 128.61, 131.29, 132.91, 133.50, 135.00, 137.81, 143.16, 190.40; MS (EI, 70 eV, for ^{79}Br): *m*/*z* (%) = 286 (5) [M], 207 (100), 105 (16), 77 (37), 51 (21).

(*E*)-3-(4-Methylphenyl)-1-phenyl-2-propen-1-one, **2e**: ^{1}H NMR ($CDCl_3$): $\delta = 2.40$ (s, 3H), 7.24 (d, 2H), 7.50 (d, $J = 15.8$ Hz, 1H), 7.48–7.61 (m, 5H), 7.81 (d, $J = 15.8$ Hz, 1H), 8.01–8.05 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 21.46$, 117.94, 121.12, 128.42, 128.53, 129.65, 132.15, 132.58, 138.35, 141.01, 144.87, 190.59; MS (EI, 70 eV): *m*/*z* (%) = 222 (33) [M], 207 (100), 145 (35), 115 (48), 105 (29), 77 (71).

(*E*)-3-(4-Methoxyphenyl)-1-phenyl-2-propen-1-one, **2f** (CAS: 959-33-1) [10]: ^{1}H NMR ($CDCl_3$): $\delta = 3.75$ (s, 3H), 6.81–6.88 (m, 2H), 7.33 (d, $J = 15.6$ Hz, 1H), 7.34–7.55 (m, 5H), 7.71 (d, $J = 15.6$ Hz, 1H), 7.91–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 55.22$, 114.31, 119.66, 127.48, 128.26, 128.41, 130.09, 132.39, 138.39, 144.52, 161.57, 190.35; MS (EI, 70 eV): *m*/*z* (%) = 238 (100) [M], 161 (58), 108 (46), 77 (86).

(*E*)-1-Phenyl-2-hexen-1-one, **2g** [11]: ^{1}H NMR ($CDCl_3$): $\delta = 0.86$ (t, $J = 7.4$ Hz, 3H), 1.44 (sex, $J = 7.4$ Hz, 2H), 2.12–2.24 (m, 2H), 6.77 (dt, $J = 15.4$ Hz, 1.0 Hz, 1H), 6.96 (dt, $J = 15.4$ Hz, 6.0 Hz, 1H), 7.30–7.48 (m, 3H), 7.80–7.86 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 13.58$, 21.27, 34.65, 125.86, 128.31, 128.32, 132.40, 137.83, 149.61, 190.68; MS (EI, 70 eV): *m*/*z* (%) = 174 (100) [M], 159 (36), 145 (100), 131 (84), 105 (100), 77 (100), 55 (100).

(*E*)-4-Methyl-1-phenyl-2-penten-1-one, **2h** [12]: ^{1}H NMR ($CDCl_3$): $\delta = 1.04$ (d, $J = 6.8$ Hz, 6H), 2.36–2.58 (m, 1H), 6.73 (dd, $J = 15.5$ Hz, 1.1 Hz, 1H), 6.95 (dd, $J = 15.5$ Hz, 6.5 Hz, 1H), 7.32–7.50 (m, 3H), 7.81–7.89 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 21.27$, 31.40, 122.97, 128.38, 128.40, 132.45, 137.98, 155.90, 191.18; MS (EI, 70 eV): *m*/*z* (%) = 174 (86) [M], 159 (53), 145 (17), 131 (26), 105 (100), 77 (100).

(*E*)-1-Phenyl-2-dodecen-1-one, **2i** (CAS: 100696-90-0) [13]: ^{1}H NMR ($CDCl_3$): $\delta = 0.81$ (t, $J = 6.7$ Hz, 3H), 1.14–1.33 (m, 12H), 1.37–1.53 (m, 2H), 2.24 (q, $J = 7.0$ Hz, 2H), 6.79 (d, $J = 15.7$ Hz, 1H), 7.00 (dt, $J = 15.7$ Hz, 6.6 Hz, 1H), 7.30–7.50 (m, 3H), 7.83–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 14.08$, 22.64, 28.13, 29.22, 29.26, 29.38, 29.46, 31.83, 32.84, 125.79, 128.45, 128.48, 132.53, 137.96, 150.21, 190.96; MS (EI, 70 eV): *m*/*z* (%) = 258 (22) [M], 159 (74), 133 (79), 120 (100), 105 (100), 77 (100), 55 (69).

(*E*)-4-(4-Chlorophenyl)-3-buten-2-one, **2j** (CAS: 3160-40-5) [14]: ^{1}H NMR ($CDCl_3$): $\delta = 2.37$ (s, 3H), 6.67 (d, $J = 16.0$ Hz, 1H), 7.33–7.50 (m, 4H), 7.47 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 27.57$, 127.44, 129.19, 129.32, 132.90, 136.37, 141.76, 197.94.

(*E*)-4-(4-Methoxyphenyl)-3-buten-2-one, **2k** (CAS: 3815-30-3) [15]: ^{1}H NMR ($CDCl_3$): $\delta = 2.35$ (s, 3H), 3.83 (s, 3H), 6.60 (d, $J = 16.3$ Hz, 1H), 6.85–6.94 (m, 2H), 7.47 (d, $J = 16.3$ Hz, 1H), 7.40–7.53 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 27.32$, 55.32, 114.37, 124.94, 126.97, 129.89, 143.21, 161.54, 198.37; MS (EI, 70 eV): *m*/*z* (%) = 176 (40) [M], 161 (100), 133 (36), 118 (18), 89 (24).

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