Intermolecular Cobalt-Mediated Pauson–Khand Reactions in Ionic Liquids

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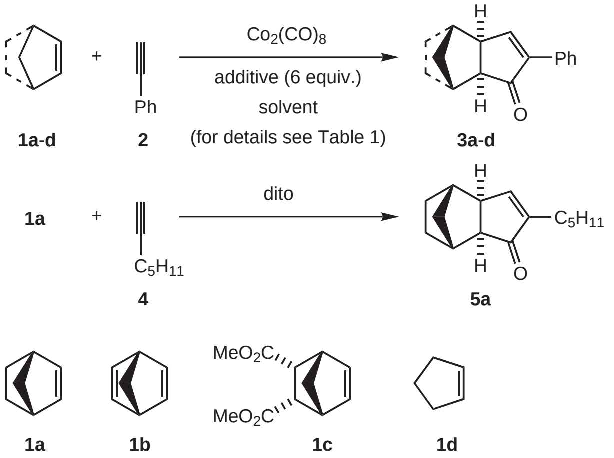
Abstract: Intermolecular Pauson–Khand reactions of strained alkenes **1a**–**d** with alkynes **2**, **4**, **6** and $Co_2(CO)_8$ were performed in [bmim]PF_6 either thermally or in the presence of NMO. For comparison thermal reactions were done in toluene and NMO-promoted reactions in CH_2Cl_2. The results show that the ionic liquid is a suitable substitute for CH_2Cl_2. Yields of the NMO-promoted reaction could be improved by using a two-phase system [bmim]PF_6/methylcyclohexane.

Keywords: Pauson–Khand reaction, ionic liquids, amine *N*-oxides

The use of room temperature ionic liquids as environmentally benign solvents in organic synthesis and organometallic catalysis has dramatically increased during the last couple of years. Particularly attractive features of ionic liquids are their non-volatility, easy recycling and their miscibility properties with water or organic solvents, which can be adjusted by proper choice of anion or cation.[2] However, despite worldwide research efforts the applicability of ionic liquids in many metal-catalyzed reactions remains unexplored.[3] Among those is the Pauson–Khand reaction, a cobalt-catalyzed [2+2+1] cocyclization of an alkene, an alkyne and carbon monoxide to give cyclopentenones.[4] We were thus interested whether intermolecular Pauson–Khand reactions could be performed either thermally or NMO-promoted in ionic liquids.[5] The results towards this goal are reported below.

As a neutral ionic liquid with a non-coordinating anion *N*-butyl-*N*-methylimidazolium hexafluorophosphate [bmim]PF_6 was chosen, which was prepared according to a procedure by Wasserscheid and Driessen–Hölscher.[6] Pauson–Khand reactions of various alkynes **1a**–**d** with phenylacetylene **2** were performed with stoichiometric amounts of $Co_2(CO)_8$ (Scheme 1, Table 1). For comparison the reactions were run in (a) toluene at 110 °C, (b) [bmim]PF_6 at 50 °C,[7] (c) CH_2Cl_2 in the presence of 6 equivalents of *N*-methylmorpholine *N*-oxide (NMO) at room temperature, and (d) [bmim]PF_6 in the presence of 6 equivalents of NMO at room temperature. After extraction with Et_2O[8] the crude cyclopentenones **3a**–**d** were purified by flash chromatography. The results in Table 1 show that indeed both thermally induced and NMO-promoted Pauson–Khand reactions are possible in [bmim]PF_6, giving the desired cyclopentenones **3** in moderate to good yields. The only exception is cyclopentene **1d**, which gaves less than 1% conversion in [bmim]PF_6 (entry 14). Direct comparison between thermal and NMO-promoted reactions in [bmim]PF_6 reveals that the ionic liquid gives higher yields in the presence of NMO for norbornene **1a** and norbornadiene **1b** (entries 2, 4, 6, 8). The use of an ionic liquid results in somewhat decreased yields as compared to conventional solvents such as toluene or CH_2Cl_2 (entries 1–4). However, upon monitoring the reactions by capillary GC good conversions were obtained in most cases (except for entries 6, 12, 14). Probably the product is partially lost during the workup procedure. This is particularly true for polar cyclopentenone **3c** derived from norbornene ester **1c**, which was isolated from the ionic liquid in only 30–32% (entries 10, 12). However, Pauson–Khand reactions were not limited to phenyl acetylene **2**. Upon treatment of 1-heptyne **4** and norbornene **1a** with $Co_2(CO)_8$ and 6 equivalents of NMO in [bmim]PF_6 for 30 minutes, the desired cyclopentenone **5a** could be isolated in 64% yield (entry 16).



Scheme 1

We wanted to address the workup problems and thus different protocols were tested. First a continuous extraction of the reaction mixture with Et_2O or EtOH was studied. Whereas Et_2O was not sufficiently polar to remove all cyclopentenone **3a** from the ionic liquid phase, EtOH as extracting solvent resulted in leaching of the ionic liquid into the organic layer. Next, the NMO-promoted reaction of norbornene **1a** and phenylacetylene **2** was performed in a two-phase system containing [bmim]PF_6 (bottom layer) and methylcyclohexane (top layer).[9] Simple extraction of the ionic liquid phase and combination of the extract with the methylcyclohexane layer allowed easy removal of the

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Table 1 Pauson–Khand Reaction of Various Alkenes **1a**–**d** with Phenylacetylene **2** or 1-heptyne **4** to the Cyclopentenones **3a**–**d**, **5a**[a]

Entry	Alkene	Alkyne	Additive	Solvent[b]	Temp.[°C]	Time [h]	Product	Conv. [%]	Yield[%]
(1)	**1a**	**2**	–	toluene	110	5	**3a**	96	81
(2)	**1a**	**2**	–	[bmim]PF_6	50	5	**3a**	94	40
(3)	**1a**	**2**	NMO	CH_2Cl_2	20	0.5	**3a**	97	92
(4)	**1a**	**2**	NMO	[bmim]PF_6	20	0.5	**3a**	96	71
(5)	**1b**	**2**	–	toluene	110	5	**3b**	90	87
(6)	**1b**	**2**	–	[bmim]PF_6	50	5	**3b**	62	54
(7)	**1b**	**2**	NMO	CH_2Cl_2	20	0.5	**3b**	94	81
(8)	**1b**	**2**	NMO	[bmim]PF_6	20	0.5	**3b**	76	73
(9)	**1c**	**2**	–	toluene	110	5	**3c**	82	59
(10)	**1c**	**2**	–	[bmim]PF_6	50	5	**3c**	84	32
(11)	**1c**	**2**	NMO	CH_2Cl_2	20	0.5	**3c**	81	76
(12)	**1c**	**2**	NMO	[bmim]PF_6	20	0.5	**3c**	35	30
(13)	**1d**	**2**	NMO	CH_2Cl_2	20	0.5	**3d**	96	40
(14)	**1d**	**2**	NMO	[bmim]PF_6	20	0.5	**3d**	1	<1
(15)	**1a**	**4**	NMO	CH_2Cl_2	20	0.5	**5a**	90	82
(16)	**1a**	**4**	NMO	[bmim]PF_6	20	0.5	**5a**	81	64
(17)	**1a**	**2**	NMO	[bmim]PF_6/MCH	20	0.5	**3a**	91	85
(18)	**1b**	**2**	NMO	[bmim]PF_6/MCH	20	0.5	**3b**	93	81
(19)	**1a**	**2**	NMO	[bmim]BF_4/MCH	20	0.5	**3a**	86	53

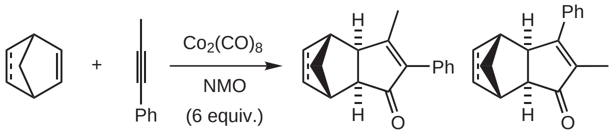
[a] Reaction conditions: alkene **1** (1.2 equiv), alkyne **2** or **4** (1.0 equiv), $Co_2(CO)_8$ (1.0 equiv), solvent, additive (6 equiv). The reactions were monitored by capillary GC. Yields refer to isolated yields.

[b] MCH refers to methylcyclohexane.

cobalt residues and yielded 85% of the desired product **3a** (entry 17). Similar results were obtained for the norbornadiene-derived product **3b** (entry 18). Unfortunately, the two-phase protocol was not successful for polar alkene **1c**. When [bmim]BF_4 instead of [bmim]PF_6 was used in the two-phase reaction of **1a** and **2**, the isolated yield of the corresponding cyclopentenone **3a** dropped down to 53% (entry 19).

In order to investigate the effect of the ionic liquid on the regioselectivity, alkenes **1a**,**b** and phenylpropyne **6** were converted in the presence of 6 equivalents of NMO either in CH_2Cl_2 or in [bmim]PF_6 to the regioisomeric cyclopentenones **7**, **8** (Scheme 2, Table 2). As shown in Table 2, the regioisomeric ratio is not effected by the ionic liquid.

In conclusion, ionic liquids such as [bmim]PF_6 are useful substitutes for CH_2Cl_2 in NMO-promoted Pauson–Khand



1a,**b** **6** **7a**,**b** **8a**,**b**

(for details see Table 2)

Scheme 2

Table 2 Pauson–Khand Reaction of Norbornene **1a** and Norbornadiene **1b** with Phenylpropyne **6** to the Regioisomeric Cyclopentenones **7**, **8**[a]

Entry	Alkene	Solvent	Products	Conv. [%]	Yield [%]	Regioisomeric ratio **7**:**8**
(1)	**1a**	CH_2Cl_2	**7a**, **8a**	99	78	96:4
(2)	**1a**	[bmim]PF_6	**7a**, **8a**	95	63	94:6
(3)	**1b**	CH_2Cl_2	**7b**, **8b**	89	88	92:8
(4)	**1b**	[bmim]PF_6	**7b**, **8b**	83	46	95:5

[a] Reaction conditions: alkene **1** (1.2 equiv), alkyne **6** (1.0 equiv), $Co_2(CO)_8$ (1.0 equiv), solvent, NMO (6 equiv), 20 °C, 30 min. The conversions and regioisomeric ratios were determined by capillary GC. Yields refer to isolated yields.

reactions regarding conversion and regioselectivity. Almost similar yields were obtained for nonpolar alkenes in a ionic liquid/methylcyclohexane two-phase system as compared to CH_2Cl_2. Attempts to overcome limitations with polar alkenes are in progress.

Thermal Pauson–Khand reactions in toluene and NMO-promoted reactions in CH_2Cl_2 were performed as described in ref.[10]

General Procedure for Thermal Pauson–Khand Reactions in Ionic Liquids:
To a solution of $Co_2(CO)_8$ (342 mg, 1.0 mmol) in [bmim]PF_6 (5 mL) was added alkyne **2**, **4** or **6** (1.00 mmol) and the resulting mixture was stirred for 40 min at r.t. Then alkene **1** (1.20 mmol) was added und the mixture was heated at 50 °C for 5 h. After cooling to r.t. the mixture was extracted with Et_2O (5 × 20 mL).[8] The combined Et_2O layers were dried over $MgSO_4$, evaporated and the crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 4:1).

General Procedure for NMO-Promoted Pauson–Khand Reactions in Ionic Liquids:
To a solution of $Co_2(CO)_8$ (342 mg, 1.0 mmol) in [bmim]PF_6 (5 mL) were sequentially added alkyne **2**, **4** or **6** (1.00 mmol), alkene **1** (1.20 mmol) and *N*-methylmorpholine *N*-oxide (705 mg, 6.00 mmol) and the resulting mixture was stirred for 30 min at r.t. The mixture was extracted with Et_2O (5 × 20 mL).[8] The combined Et_2O layers were dried over $MgSO_4$, evaporated and the crude product was purified by flash chromatography (SiO_2, hexane/EtOAc 4:1).

General Procedure for NMO-Promoted Pauson–Khand Reactions in Ionic Liquid/Methylcyclohexane Two-Phase System:
To a solution of $Co_2(CO)_8$ (342 mg, 1.0 mmol) in [bmim]PF_6 (5 mL) and methylcyclohexane (5 mL) were sequentially added alkyne **2** (1.00 mmol), alkene **1** (1.20 mmol) and *N*-methylmorpholine *N*-oxide (705 mg, 6.00 mmol) and the resulting mixture was stirred for 30 min at r.t. The mixture was diluted with methylcyclohexane (80 mL) and the layers were separated. The ionic liquid layer was extracted with Et_2O (5 × 20 mL) and EtOH (5 × 20 mL) and the combined organic layers (including the methylcyclohexane layer) were combined, dried over $MgSO_4$, evaporated.

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