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Gold-catalyzed hydrative cyclization of 1,6-diynes in ionic liquid media

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ABSTRACT

Gold-catalyzed hydrative cyclization of terminal 1,6-diynes proceeds in ionic liquid with methanol as co-solvent. The solvent-catalyst could be recycled, after separation of the product by extraction with ether.

The cyclohexenone derivatives are the starting materials and intermediates in many important natural products and synthetic drug syntheses.[1] Many synthetic methods for the construction of the conjugate cyclohexenone ring have been reported.[2] We have recently developed hydrative cyclization of 1,6-diynes to produce 3,5-substituted conjugate cyclohexenone ring systems using $(PPh_3)AuMe$/acid as a catalyst.[3] However, the reactions were not feasible for the separation of products and catalyst, and the catalyst which is recovered and reused is still problematic as in other homogeneous catalytic reactions. On the other hand, ionic liquids have attracted much attention due to their special properties such as almost undetectable vapor pressure, wide liquid temperature range, excellent chemical stability, high thermal stability, and strong solvent power for a wide rang of organic, inorganic, and polymeric molecules.[4] Some ionic liquids as a class of new media of considerable potential have been successfully exploited as alternatives to molecular solvents in transition metal-catalyzed reaction such as hydrogenation, isomerization, hydroformylation, dimerization of but-1,3-ene, hydroesterification, Heck reaction, epoxidation, polymerization of methyl methacrylate, and Suzuki cross-coupling reaction.[5] We report herein Au-catalyzed hydrative cyclization of 1,6-diynes carried out in ionic liquids to synthesize cyclohexenones.

The hydrative cyclization of 1,6-diyne **1a** (0.5 mmol) with H_2O (0.5 mmol) was first performed using 1-butyl-3-methylimidazolium tetrafluoroborate ($[bmim]BF_4$) (1 mL) as hydrophilic ILs and methanol (1 mL) as the co-solvent mixture in the presence of a catalytic amount of $(PPh_3)AuNO_3$ (5 mol %) and methanesulfonic acid (CH_3SO_3H) (50 mol %) at 70 °C. Under these conditions, the hydrative cyclization worked efficiently to form cyclohexenone **2a** in 78% yield (Table1, entry 3). Decreasing the concentration of methanol within the examined range, however, showed lower yield (Table 1, entry 2). The reaction did not proceed in the absence of methanol (Table1, entry 1). Different ILs were screened, the reaction gave mild yields using 1-hexyl-3-methlimidazolium hexafluorophosphate ($[hmim]PF_6$) as hydrophobic ILs and using 1,3-dimethylimldazolium methylsulfate ([mmim]OMs) gave poor result (Table1, entries 10 and 11). The reaction was smoothly realized at lower catalyst loadings and acidic promoter (Table 1, entries 4–6). The workup of the reaction mixture was a non-trivial operation for the reactions carried out in ILs. Although ethyl acetate appeared to be the solvent of choice for the efficient extraction of the product **2a**, small amounts of the ILs were extracted by the solvent. To this end, the reaction mixture was extracted with diethyl ether, which requires several times, the partial loss of these costly ILs solvents can be avoided.

In order to demonstrate the efficiency and scope of the present method, we applied the optimum condition to the hydrative cyclization of several 1,6-diyne substrates bearing a variety of functionalities. The results are summarized in Table 2. The reaction tolerated both acid- and base-sensitive functional groups such as esters and ethers. Terminal malonate derivatives **1a** and **1b** were found to serve as good substrates in ILs-MeOH co-solvent system; yields are similar to those obtained from the syntheses in which methanol was used as a reaction media (Table 2, entries 1 and 2).[3] Ketone derivatives **1c** and **1d**, which failed to undergo Au-catalyzed hydrative cyclization in methanol as solvent, were transformed into cyclic products **2c** and **2d** (Table 2, entries 3 and 4). In contrast to using molecular solvents in ILs bearing unprotected hydroxyl groups in diynes were also tolerated, thus offering unprotected hydroxyl groups in the cyclohexenone with no intramolecular alcohol additive products (Table 2, entries 6, 8, 9, and 11).[6] The cyclic product with different substituted group pairs, such as diphenylphosphoryl and ethoxycarbonyl **2g**, was obtained in good yield (Table 2, entry 7). In our hand, spirocyclic compounds **2m** and **2n** bearing a fluorene moiety were successfully obtained from diynes **1m** and **1n** in 75% and 65% yields, respectively (Table 2, entries 13 and 14). In addition, the internal diynes **1o** afforded the different cyclic product **2o** (Table 2, entry 15). The same gold-catalyzed cyclization reaction of disubstituted 1,6-diynes has recently been reported.[7]

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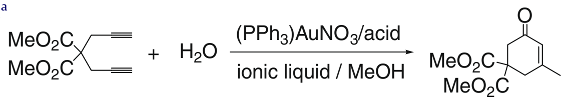
Table 1
Hydrative cyclization of 1,6-diyne **1a** in ionic liquid[a]

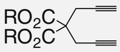
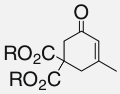
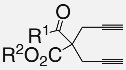
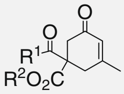
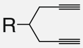
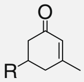
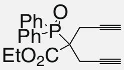
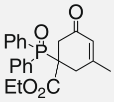
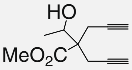
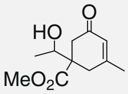
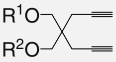
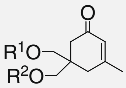
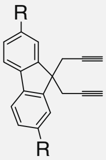
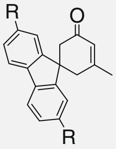
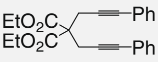
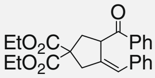


1a **2a**

Entry	Au (mol %)	MeSO$_3$H (mol %)	ILs (mL)	MeOH (mL)	Time (h)	Yield[b] (%)
1	5	50	[bmim]BF$_4$ (2)	–	3	Trace
2	5	50	[bmim]BF$_4$ (1)	0.5	1.5	25
3	5	50	[bmim]BF$_4$ (1)	1	3	78
4	2	50	[bmim]BF$_4$ (1)	1	3	72
5	1	50	[bmim]BF$_4$ (1)	1	3	65
6	2	25	[bmim]BF$_4$ (1)	1	3	71
7	2	10	[bmim]BF$_4$ (1)	1	3	44
8	5	–	[bmim]BF$_4$ (1)	1	3	Trace
9	5	50	[bmim]BF$_4$ (1)	1	3	76
10	5	50	[hmim]PF$_6$ (1)	1	4.5	53
11	5	50	[mmim]OMs (1)	1	4	25
12	5	50	[bmimBF$_4$ (1)	1	3	78
13	5	50	[bmim]PF$_4$ (0.5)	1.5	4.5	57
14	5	75	[bmimBF$_4$ (1)	1	4.5	49

[a] The reactions were performed with **1a** (0.5 mmol), H_2O (0.5 mmol), MeSO$_3$H (0–75 mol %), and catalyst (1–5 mol %) in ionic liquid and MeOH at 70 °C.
[b] Isolated yields.

Table 2
Au (I)-catalyzed hydrative cyclization of 1,6-diynes in ionic liquid[a]

Entry	1,6-Diyne	1	Time (h)	Product	2	Yield[b] (%)
1		**1a**: R = Me	3		**2a**	72
2		**1b**: R = Et	3		**2b**	82
3		**1c**: R^1 = Me; R^2 = Me	4		**2c**	65
4		**1d**: R^1 = Ph; R^2 = Et	4.5		**2d**	60
5		**1e**: R = CO$_2$Et	3		**2e**: R = CO$_2$Me	67
6		**1f**: R = CH$_2$OH	3		**2f**	91
7		**1g**	3		**2g**	73
8		**1h**	4.5		**2h**	52
9		**1i**: R^1 = H; R^2 = H	3.5		**2i**	54
10		**1j**: R^1 = Me; R^2 = Me	1		**2j**	96
11		**1k**: R^1 = allyl; R^2 = H	5		**2k**	71
12		**1l**: R^1 = allyl; R^2 = allyl	15		**2l**	83
13		**1m**: R = H	3		**2m**	75
14		**1n**: R = Cl	3.5		**2n**	63
15		**1o**	3		**2o**	80

[a] The reactions were performed with 1,6-diyne 1 (0.5 mmol), H_2O (0.5 mmol), MeSO$_3$H (50 mol %), and (PPh$_3$)AuNO$_3$ (5 mol %) in [bmim]BF$_4$ (1 mL) and MeOH (1 mL) at 70 °C.
[b] Isolated yields.

Table 3

Ionic liquid and catalyst recycling in hydrative cyclization of **1a**[a]

Entry	1	2	3	4	5	6
Yield[b] (%)	78	74	76	76	72	75

[a] The reactions were performed with **1a** (0.5 mmol), H_2O (0.5 mmol), $MeSO_3H$ (50 mol %), and $(PPh_3)AuNO_3$ (5 mol %) in $[bmim]BF_4$ (1 mL) and MeOH (1 mL) at 70 °C for 3 h.

[b] Isolated yields.

Moreover, we attempted a recycling of the ILs-catalyst system. After 3 h at 70 °C, the mixture was extracted with diethyl ether, dried under vacuum, and added to the same amount of diynes, H_2O, $MeSO_3H$, and MeOH. We showed that ILs containing the gold catalyst can be reused five times without any loss of activity. Examples of the reaction carried out in the recycled $[bmim]BF_4$ are presented in Table 3. The yields of cyclohexenone were basically similar to those observed using fresh non-recycled ionic liquid.

We have shown that hydrative cyclization of 1,6-diynes proceeds in ionic liquid media which acts as an excellent co-solvent.[8] The gold catalyst in the ionic liquid could be recycled in five subsequent reactions without the loss of the reaction efficiency. The good yields were observed for a variety of terminal diynes.

Acknowledgment

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8. *General procedure for the hydrative cyclization of diynes in ionic liquids*: To a reactor containing diyne (0.5 mmol), methanol (1 mL), ionic liquids (1 mL), and H_2O (0.5 mmol) were added $(Ph_3P)Au\ NO_3$ (5 mol %) and CH_3SO_3H (50 mol %) under nitrogen. The resulting yellow solution was then sealed and stirred at 70 °C until the starting diyne was consumed as judged by TLC. Methanol was removed and diethyl ether (5 × 2 mL) was added to the contents and stirred. The supernatant diethyl ether layer containing the product was decanted. The diethyl ether layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel) to yield cyclized product in an analytically pure form. The recovered ionic liquid containing the gold catalyst was concentrated in vacuo and was reused in the next run.