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ORIGINAL PAPER

Lewis basic ionic liquid as an efficient and facile catalyst for acetylation of alcohols, phenols, and amines under solvent-free conditions

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Abstract The Lewis basic ionic liquid 1,8-diazabicyclo[5.4.0]undec-7-en-8-ium acetate was employed for the acetylation of various phenols, alcohols, and amines in good-to-excellent yields at 50 °C under solvent-free conditions in a short time. Compared with existing methods based on conventional catalysts and toxic solvents, the reported method is simple, mild and environmentally viable. Furthermore, the ionic liquid was conveniently separated from the products and easily recycled to catalyze other acetylation reactions with excellent yields.

Keywords Ionic liquid · [HDBU]OAc · Acetylation · Phenol · Amine · Solvent-free condition

Introduction

The protection of heteroatoms—especially those in hydroxyl and amino groups—as acetyl derivatives is one of the most frequent transformations used in organic synthesis because deprotection is relatively easy to achieve [1, 2]. Typically, the protection of alcohols or phenols as acetate esters and amines as acetamides is realized using acetyl chloride or acetic anhydride in the presence of a basic catalyst such as triethylamine or pyridine. In addition, 4-(dimethylamino) pyridine (DMAP) [3] has been used as an efficient catalyst of acetylation. Other catalysts employed for acylation include nucleophilic agents such as Bu_3P [4], Lewis acids such as metal halides [5–9], metal triflates [10, 11], perchlorates [12–14], fluoroboric acid derivates [15, 16], metal triflimide [17], ionic liquids [18–20], and several solid acids such as zeolite [21], Nafion-H [22], and $HClO_4$–SiO_2 [23]. Most of the above can be used for the acetylation of various acid/base-sensitive substrates. However, previously reported methods suffer from at least one of the following disadvantages: long reaction time; harsh reaction conditions; a need for expensive, moisture-sensitive, and toxic reagents as well as toxic solvents; and the formation of side products. For example, DMAP is highly toxic (its LD_{50} value is 56 mg/kg), Bu_3P is flammable (its flash point is 37 °C) and air sensitive, perchlorates are explosive, and triflates are expensive and moisture sensitive. Many catalysts such as Nafion-H and *N*-heterocyclic carbenes require special conditions for their preparation or are a potential health hazard. Therefore, there is increasing demand for new catalysts that can help to overcome the challenges mentioned above, and it is necessary to develop a mild, efficient, and environmentally benign acylation reaction.

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was found to be a far superior catalyst compared to other tertiary amines, and its nucleophilic nature and utility in organic synthesis have also been investigated over the past decades. Recently, Birman et al. [24, 25] successfully introduced nonaromatic amidine derivatives, including DBU, as catalysts for acylation reactions. However, the associated procedure suffered from low recyclability and the unpleasant flavor of DBU, which conflicted with the concept of green chemistry. Thus, a new basic ionic liquid, 1,8-diazabicyclo[5.4.0]undec-7-en-8-ium acetate ([HDBU]OAc), was synthesized through the neutralization reaction of DBU

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and acetic acid. This DBU salt is a ionic liquid with weak basicity at room temperature. [HDBU]OAc has been used for various organic transformations because of its ease of preparation and high activity [26–28]. The main aim of the work described in this paper was to employ [HDBU]OAc to catalyze the acetylation of alcohols, phenols, and amines under mild conditions.

Results and discussion

Effect of the solvent

Initially to optimize the reaction conditions, we tried to convert 4-nitrophenol (10.0 mmol) to 4-nitrophenyl acetate in the presence of a catalytic amount of [HDBU]OAc (20 mol%) and acetic anhydride (10.1 mmol) in various solvents and also under solvent-free conditions. As shown in Table 1, in comparison to conventional methods performed in solvents such as 1,2-dichloroethane, acetonitrile, toluene, THF, and *n*-hexane, the yield of the reaction realized under solvent-free conditions is higher and the reaction time is shorter. Therefore, we employed solvent-free conditions for the conversion of various alcohols, phenols, and amines to the corresponding acetates or acetamides.

Effect of the amount of [HDBU]OAc

The amount of [HDBU]OAc was varied from 5 to 30 mol% to study its effect on the acetylation of 10.0 mmol 4-nitrophenol with 10.1 mmol acetic anhydride (Table 2). The reactions were carried out with 5, 10, 15, 20, 25, and 30 mol% of [HDBU]OAc. The yield of 4-nitrophenyl acetate was measured after 0.75 h of stirring the mixture at 50 °C. We observed that the yield increased rapidly as the amount of [HDBU]OAc was increased (up to 20 mol%), and then slowed down. These results show that the reaction of [HDBU]OAc and acetic anhydride could be the rate-limiting step when a small amount of [HDBU]OAc is available (<20 mol%). However, when the amount of [HDBU]OAc increases (more than 30 mol%), the acetylation of substrates becomes the rate-limiting step. Therefore, we decided to use 20 mol% [HDBU]OAc in subsequent experiments.

Table 1 Effect of the solvent during the [HDBU]OAc-catalyzed acetylation of 4-nitrophenol with Ac_2O using different solvents

Entry	Solvent	Time/h	Yield[a]/%
1	1,2-Dichloroethane	2	68
2	Acetonitrile	2	25
3	Toluene	2	11
4	THF	2	62
5	*n*-Hexane	2	16
6	Neat	0.75	97

The substrate was treated with Ac_2O (1.01 equiv.) and [HDBU]OAc (0.20 equiv.) at 50 °C

[a] Yield determined by GC

Table 2 Yield of the acetylation of 4-nitrophenol with different amounts of [HDBU]OAc

Entry	Cat./mol%	Time/h	Yield[a]/%
1	–	2.0	5
2	20[b]	2.0	82
3	20[c]	2.0	8
4	5	0.75	22
5	10	0.75	35
6	15	0.75	78
7	20	0.75	95
8	25	0.75	95
9	30	0.75	96

The substrate was treated with Ac_2O (1.01 equiv.) at 50 °C

[a] Yield determined by GC

[b] The catalyst was replaced with DBU

[c] The catalyst was replaced with HOAc

Effect of the reaction temperature

The reaction temperature was varied from 20 to 70 °C to study its effect on the acetylation of 10.0 mmol 4-nitrophenol with 10.1 mmol acetic anhydride (Table 3). The reactions were carried out at 20, 30, 40, 50, 60, and 70 °C. We observed that the yield increased rapidly as the temperature was increased (up to 50 °C). When the temperature was higher than 60 °C, the substrate transformed into acetate rapidly with a violent release of heat and the yield decreased slightly, probably due to the partial

Table 3 Yield of the acetylation of 4-nitrophenol at different reaction temperatures

Entry	Temperature/°C	Time/h	Yield[a]/%
1	20	2.0	5
2	30	2.0	45
3	40	1.0	85
4	50	0.75	95
5	60	0.40	93
6	70	0.20	90
7	80	0.10	87

The substrate was treated with Ac_2O (1.01 equiv.) and [HDBU]OAc (0.20 equiv.)

[a] Yield determined by GC

volatilization of acetic anhydride and the occurrence of some side reactions at higher reaction temperatures. Based on these results and the generality of the method, 50 °C was chosen for further experiments.

Reusability of the catalyst

The reusability of the catalyst was also investigated. For this purpose, the same model reaction was studied again under optimized conditions. After the completion of the reaction, the reaction mixture was cooled to room temperature and diluted with diethylether and water. The aqueous layer was concentrated under reduced pressure to remove the acetic acid and water, and the catalyst [HDBU]OAc was recovered as an oily residue and reused for a similar reaction after drying in vacuo. As shown in Fig. 1, the catalyst could be reused at least five times without any significant loss of activity.

Acetylation of alcohols, phenols, and amines

To explore the generality and scope of the method, various phenols, primary, secondary, and benzylic alcohols, and amines with various groups were acetylated with acetic anhydride using the optimized reaction conditions (Scheme 1), and the results are listed in Table 4. No competitive Fries rearrangement was observed for phenolic substrates (entries 1–7), which is very common in the presence of a Lewis acid. Catechol and hydroquinone were also not oxidized to the corresponding benzoquinones (entries 9, 10). Prenyl alcohol, an allylic alcohol, was transformed to the corresponding acetate without affecting the carbon–carbon double bond (entry 16), and benzylic alcohol was acetylated without the formation of any oxidative side products (entry 17). The efficacy of the catalyst can be clearly visualized in the acetylation of polyhydroxy compounds under similar conditions (entries 14, 15, 19, 30). Obviously, the acetylation of amines was much faster than that of alcohols and phenols, which may be due to the higher nucleophilicity of amines than phenols (entries 20–29). Another noteworthy feature of this methodology is that carbohydrates such as D-glucose and valienamine underwent exhaustive acetylation (entries 19, 30), demonstrating the practical utility of this method in carbohydrate chemistry and pharmaceutical chemistry.

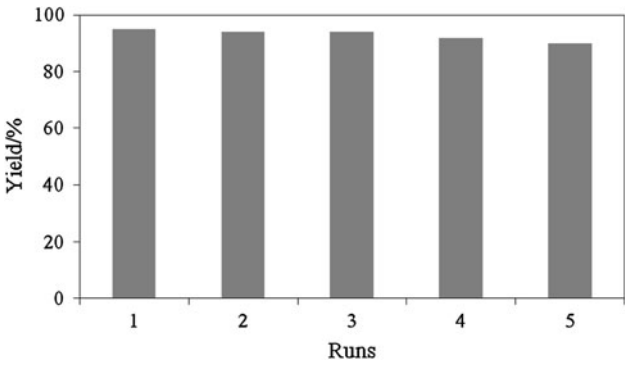
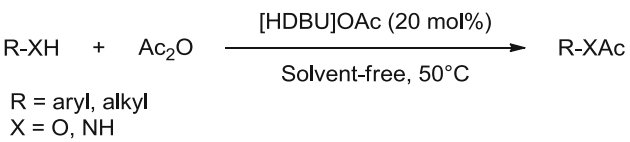


Fig. 1 Reuse of [HDBU]OAc for the acetylation of 4-nitrophenol under optimized conditions



Scheme 1

The possible mechanism of acetylation catalyzed by [HDBU]OAc

Based on all of the results that obtained above, we pinpointed the catalysis cycle is shown in Scheme 2, which is similar to the mechanism of acetylation catalyzed by pyridine and DMAP [48].

Conclusion

In summary, [HDBU]OAc was found to be a new, highly efficient, and chemoselective catalyst for the acylation of primary and secondary alcohols, phenols, and amines. Given the continual tightening of legislation on the release of waste and use of toxic substances as a measure to control environmental pollution, the use of a stoichiometric amount of acetylating agent and the solvent-free conditions employed in the present method make it environmentally friendly and suitable for industrial applications.

Experimental

All chemicals were of reagent grade and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopic data (^{1}H NMR and ^{13}C NMR spectra) and melting points. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker (Karlsruhe, Germany) AC-P400 spectrometer. The spectra were measured in $CDCl_3$, relative to TMS (0.00 ppm). GC analysis was performed using an Agilent (Santa Clara, CA, USA) 1705A GC. All reactions were carried out in predried glassware (150 °C, 5 h) cooled under a vacuum. The Lewis basic ionic liquid [HDBU]OAc was prepared according to a method described in a previous work [20].

Table 4 [HDBU]OAc-catalyzed acetylation of phenols, alcohols, amines, and sugars

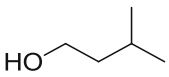
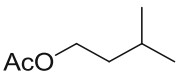
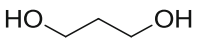
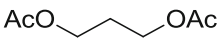
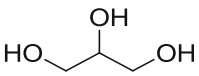
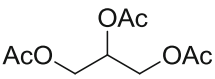
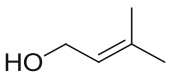
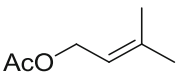
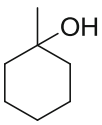
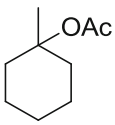
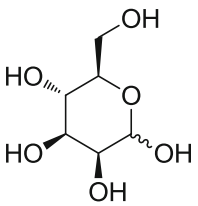
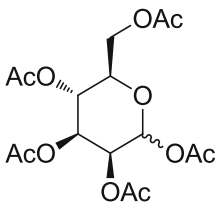
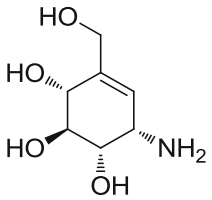
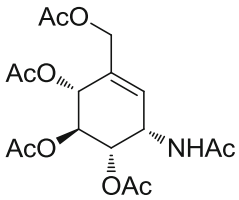
Entry	Substrates	Products[a]	Yield[b]/%	Time/h	Ref.
1	PhOH	PhOAc	94	0.75	[29]
2	*p*-NO_2-PhOH	*p*-NO_2-PhOAc	95	0.75	[29]
3	*o*-NO_2-PhOH	*o*-NO_2-PhOAc	94	0.75	[17]
4	*p*-Cl-PhOH	*p*-Cl-PhOAc	94	0.75	[29]
5	*p*-Me-PhOH	*p*-Me-PhOAc	90	0.75	[29]
6	*p*-(*t*-Bu)-PhOH	*p*-(*t*-Bu)-PhOAc	91	0.75	[29]
7	2,6-(*t*-Bu)$_2$-PhOH	2,6-(*t*-Bu)$_2$-PhOAc	90	0.75	[30]
8	2,4-$(NO_2)_2$-PhOH	2,4-$(NO_2)_2$-PhOAc	89	1.0	[31]
9[c]	1,2-$(HO)_2C_6H_4$	1,2-$(AcO)_2C_6H_4$	95	1.0	[29]
10[c]	1,4-$(HO)_2C_6H_4$	1,4-$(AcO)_2C_6H_4$	96	1.0	[32]
11	*n*-BuOH	*n*-BuOAc	88	1.0	[33]
12	*t*-BuOH	*t*-BuOAc	85	1.5	[29]
13			87	1.0	[34]
14[c]			91	1.5	[35]
15[d]			92	1.5	[36]
16			86	1.0	[37]
17	BnOH	BnOAc	92	1.0	[19]
18			89	1.0	[23]
19[e]			95	3.0	[38]
20	$BnNH_2$	BnNHAc	92	0.5	[39]
21	$PhNH_2$	PhNHAc	95	0.5	[40]
22	*p*-Me-$PhNH_2$	*p*-Me-PhNHAc	94	0.5	[40]
23	*o*-Me-$PhNH_2$	*o*-Me-PhNHAc	93	0.5	[40]
24	*o*-NO_2-$PhNH_2$	*o*-NO_2-PhNHAc	95	0.5	[41]
25	*m*-MeO-$PhNH_2$	*m*-MeO-PhNHAc	96	0.5	[42]
26	*o*-CF_3-$PhNH_2$	*o*-CF_3-PhNHAc	96	0.5	[43]
27	*o*-Cl-$PhNH_2$	*o*-Cl-PhNHAc	93	0.5	[44]

Table 4 continued

Entry	Substrates	Products[a]	Yield[b]/%	Time/h	Ref.
28	*p*-Cl-PhNH$_2$	*p*-Cl-PhNHAc	94	0.5	[45]
29	*p*-F-PhNH$_2$	*p*-F-PhNHAc	96	0.5	[46]
30[e]			92	2.0	[47]

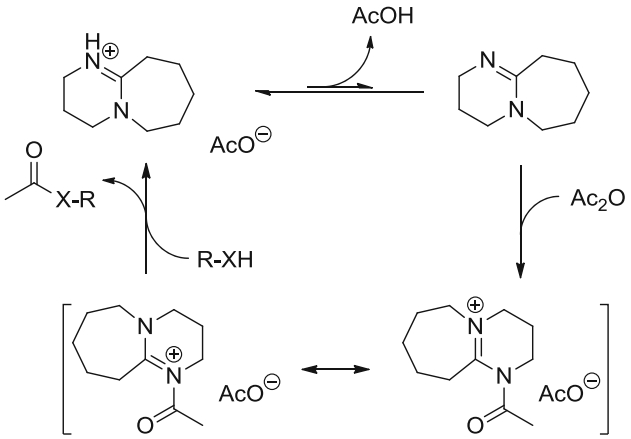
[a] All products were identified by their ^{1}H NMR and ^{13}C NMR spectra. All spectral data and melting point data for solid products are provided in the "Electronic supplementary material"

[b] Yields of the corresponding acetylated products refer to isolated yields obtained at 50 °C using [HDBU]OAc (0.20 equiv.) and Ac_2O (1.01 equiv.), except in special cases

[c] Reaction carried out with 2.02 equivalents of Ac_2O

[d] Reaction carried out with 3.03 equivalents of Ac_2O

[e] Reaction carried out with 5.05 equivalents of Ac_2O



Scheme 2

Typical procedure for acetylation using [HDBU]OAc

To a stirred solution of 1.39 g 4-nitrophenol (10 mmol) in 1.03 g of freshly distilled acetic anhydride (10.1 mmol) were added 0.42 g of [HDBU]OAc (20 mol%), and the reaction mixture was stirred at 50 °C for 45 min. The reaction was monitored by TLC (EtOAc/hexane = 1:4, v/v) and GC. After the reaction had completed, the mixture was diluted with EtOAc and water. The organic layer was washed with saturated $NaHCO_3$ solution and water and then dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give an oil, which was purified by column chromatography (EtOAc/hexane = 1:15, v/v) if necessary. The aqueous layer was concentrated under reduced pressure to remove the acetic acid and water, and the catalyst [HDBU]OAc was recovered as a pale yellow oily residue that could be reused after drying in vacuo at 80 °C for 12 h.

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References

1. Greene TW, Wuts PGM (1999) Protective groups in organic synthesis, 3rd edn. Wiley, New York
2. Hanson JR (1999) Protective groups in organic synthesis. Blackwell, Malden
3. Steglich W, Hofle G (1969) Angew Chem Int Ed 8:981
4. Vedejs E, Bennett NS, Conn LM, Diver ST, Gingras M, Lin S, Oliver PA, Peterson MJ (1993) J Org Chem 58:7286
5. Torregiani E, Seu G, Minassi A, Appendino G (2005) Tetrahedron Lett 46:2193
6. Bhattacharya AK, Diallo MA, Ganesh KN (2008) Synth Commun 38:1518
7. Meshram G, Patil VD (2009) Synth Commun 39:4384
8. Chakraborti AK, Gulhane R (2004) Synlett 15:627
9. Chakraborti AK, Gulhane R (2003) Tetrahedron Lett 44:6749
10. Kamal A, Khan MNA, Reddy KS, Srikanth YVV, Krishnaji T (2007) Tetrahedron Lett 48:3813
11. Shirini F, Zolfigol MA, Aliakbar AR, Albadi J (2010) Synth Commun 40:1022
12. Bartoli G, Bosco M, Dalpozzo R, Marcantoni E, Massaccesi M, Sambri L (2003) Eur J Org Chem 4611
13. Chakraborti AK, Sharma L, Gulhane R, Shivani (2003) Tetrahedron 59:7661
14. Chakraborti AK, Gulhane R, Shivani (2003) Synlett 1805
15. Chakraborti AK, Gulhane R (2003) Tetrahedron Lett 44:3521
16. Chakraborti AK, Gulhane R, Shivani (2004) Synthesis 111
17. Chakraborti AK, Shivani (2006) J Org Chem 71:5785
18. Wang WJ, Cheng WP, Shao LL, Yang JG (2008) Catal Lett 121:77

19. Hajipour AR, Khazdooz L, Ruoho AE (2009) J Chin Chem Soc 56:398
20. Yue CB, Liu QQ, Yi TF, Chen Y (2010) Monatsh Chem 141:975
21. Ballini R, Bosica G, Carloni S, Ciaralli L, Maggi R, Sartori G (1998) Tetrahedron Lett 39:6049
22. Kumareswaran R, Pachamuthu K, Vankar YD (2000) Synlett 1652
23. Chakraborti AK, Gulhane R (2003) Chem Commun 1896
24. Birman VB, Li XM, Han ZF (2007) Org Lett 9:37
25. Yang X, Birman VB (2009) Org Lett 11:1499
26. Ying AG, Liu L, Wu GF, Chen G, Chen XZ, Ye WD (2009) Tetrahedron Lett 50:1653
27. Ying AG, Wang LM, Wang LL, Chen XZ, Ye WD (2010) J Chem Res 30
28. Yang ZZ, He LN, Miao CX, Chanfreau S (2010) Adv Synth Catal 352:2233
29. Das R, Chakraborty D (2011) Synthesis 1621
30. Simion AM, Hashimoto I, Mitoma Y, Egashira N, Simion C (2011) Synth Commun 42:921
31. Neuvonen H, Neuvonen K, Koch A, Kleinpeter E, Pasanen P (2002) J Org Chem 67:6995
32. Zarei A, Hajipour AR, Khazdooz L (2011) Synth Commun 41:1772
33. Iuchi Y, Obora Y, Ishii Y (2010) J Am Chem Soc 132:2536
34. Chakraborti AK, Singh B, Chankeshwara SV, Patel AR (2009) J Org Chem 74:5967
35. Tanoue Y, Hamada M, Kai N, Nagai T, Sakata K, Hashimoto M, Morishita SI (2000) J Heterocycl Chem 37:1351
36. Satam JR, Gawande MB, Deshpande SS, Jayaram RV (2007) Synth Commun 37:3011
37. Dubovyk I, Watson IDG, Yudin AK (2007) J Am Chem Soc 129:14172
38. Grugel H, Minuth T, Boysen MMK (2010) Synthesis 3248
39. Barbero M, Bazzi S, Cadamuro S, Dughera S (2009) Eur J Org Chem 430
40. Lee YM, Moon ME, Vajpayee V, Filimonov VD, Chi KW (2010) Tetrahedron 66:7418
41. dos Santos CMG, McCabe T, Watson GW, Kruger PE, Gunnlaugsson T (2008) J Org Chem 73:9235
42. Karimi B, Behzadnia H (2010) Synlett 2019
43. Strekowski L, Patterson SE, Janda L, Wydra RL, Harden DB, Lipowska M, Cegla MT (1992) J Org Chem 57:196
44. Bedford RB, Engelhart JU, Haddow MF, Mitchell CJ, Webster RL (2010) Dalton Trans 39:10464
45. Liu LF, Liu H, Pi HJ, Yang S, Yao M, Du WT, Deng WP (2011) Synth Commun 41:553
46. Kajihara K, Arisawa N, Shuto S (2008) J Org Chem 73:9494
47. Shing TKM, Li TY, Kok SHL (1999) J Org Chem 64:1941
48. Xu SJ, Held I, Kempf B, Mayr H, Steglich W, Zipse H (2005) Chem Eur J 11:4751