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ORIGINAL ARTICLE

One-pot solvent-free rapid and green synthesis of 3,4-dihydropyrano[c]chromenes using grindstone chemistry

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Abstract An easy solvent-free method is described for the synthesis of 3,4-dihydropyrano[c]chromenes by a one pot three component coupling reaction of aromatic aldehydes, malononitrile, and 4-hydroxycoumarin using basic ionic liquid as the catalyst by grindstone chemistry. The salient features of this one pot protocol are short reaction times, cleaner reaction profiles and simple workup.

1. Introduction

3,4-Dihydropyrano[c]chromene derivatives have recently attracted the attention of synthetic and medicinal chemists because of their wide range of biological and pharmaceutical activities such as diuretic, analgesic, myorelaxant (Bonsignore et al., 1993), anticoagulant (Cingolani et al., 1969), anticancer (Wu et al., 2003), anti-tumor (Baraldi et al., 1992; Perrella et al., 1994), and anti-HIV (Kashman et al., 1992; Patil et al., 1993). They are also used as cognitive enhancers, for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, AIDS associated dementia, Down's syndrome and schizophrenia and myoclonus (Konkoy et al., 2000). These derivatives constitute numerous natural products like calanolides, calanone, calophyllolides etc. (Rueping et al., 2008).

They have been synthesized in the presence of a variety of catalysts such as DBU (Khurana et al., 2010), TBAB (Khurana and Kumar, 2009), diammonium hydrogen phosphate (Abdolmohammadi and Balalaie, 2007), heteropoly acids (Heravi et al., 2009), nano ZnO (Paul et al., 2011), KAl $(SO_4)_2{\cdot}12H_2O$ (Karimi and Sedaghatpour, 2010), TMGT (Shaabani et al., 2005), MgO (Seifi and Sheibani, 2008), K_2CO_3 (Kidwai and Saxena, 2006), pyridine (Shaker, 1996), [bmim]OH (Gong et al., 2009), and Morpholine (Heravi et al., 2011). However, many of these methods are associated with several disadvantages such as long reaction time, drastic reaction conditions, difficult catalyst recovery, very expensive reagents, low yields and tedious workup. It was thought momentous to find a simple, inexpensive and reusable catalyst for the synthesis of 3,4-dihydropyrano[c]chromenes as our group is actively engaged in exploring the new facets of heterocyclic synthesis (Dadhania et al., 2011, 2012a,b; Patel et al., 2012; Avalani et al., 2012; Tarpada et al., 2016).

Solid-state syntheses have recently received much attention. These processes have many advantages such as high efficiency and selectivity, easy separation, purification and mild reaction

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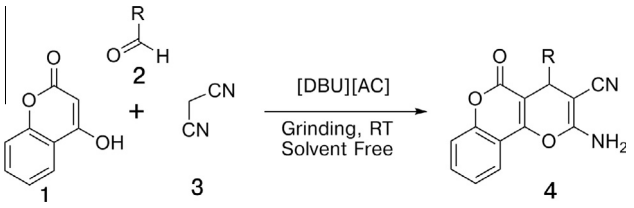

Scheme 1 Synthesis of 3,4-dihydropyrano[c]chromenes.

Table 1 The effect of different amounts of [DBU][AC] on the reaction of 4-hydroxycoumarin, 4-chlorobenzaldehyde and malononitrile.

Entry	IL (mol%)	Time (min)	Yield (%)
1	0	30	No reaction
2	1.53	15	64
3	3.03	5	93
4	4.62	5	92
5	6.06	5	90

conditions (Tanaka and Toda, 2000). They are not only environmentally benign, but also economically beneficial because toxic wastes can be minimized or eliminated. The grinding mode for the solid-state reactions has earlier been employed for Grignard reaction (Takumi and Toda, 1989), Reformatsky reaction (Tanaka et al., 1991), aldol condensation (Toda et al., 1990), Dieckmann condensation (Toda et al., 1998), Knoevenagel condensation (Ren et al., 2002), reduction (Toda et al., 1989) and other reactions (Ren et al., 2004, 2005; Schmeyers et al., 1998).

All these facts have prompted us to achieve the multicomponent synthesis of 3,4-dihydropyrano[c]chromenes at room temperature using ionic liquid [DBU][Ac] as catalyst by the grinding method under solvent-free condition (Scheme 1).

2. Experimental

2.1. General

All chemicals used were of commercial grade and were used without any further purification. Melting points were determined using a μThermoCal$_{10}$ (Analab scientific Pvt. Ltd.) melting point apparatus and are uncorrected. TLC was carried out using aluminum sheets precoated with silica gel 60 F_{254} (Merck). IR spectra were recorded on a FTIR Perkin Elmer Spectrum 100 spectrometer. Elemental analysis was performed on a Perkin Elmer PE 2400 elemental analyzer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz instrument with TMS as an internal standard.

2.2. General procedure for preparation of ionic liquid [DBU][Ac]

Aliquot of acetic acid (1 equiv.) was added over a period of 15 min to DBU (1 equiv.) at 5 °C in an ice bath under ultrasound. The reaction mixture was irradiated under ultrasound for an additional period of 15 min at ambient temperature. Thus obtained oily residue was dried *in vacuo* at 60 °C for 1 h to afford [DBU][Ac] a light yellow viscous liquid. This was characterized by ^{1}H NMR and ^{13}C NMR.

^{1}H NMR (400 MHz, D_2O): δ:1.766 (s, 3H, CH_3), 1.517–1.671 (m, 6H, 3-H, 4-H, 5-H), 1.842–1.901 (m, 2H, 10-H), 2.394–2.650 (m, 2H, 6-H), 3.164–3.193 (m, 2H, 2-H), 3.278–3.437 (m, 4H, 11-H, 9-H) ppm; ^{13}C NMR (100 MHz, D_2O): δ: 19.50, 23.34, 25.86, 27.34, 28.42, 32.76, 37.96, 48.20, 54.12, 165.94, 179.43 ppm.

2.3. Representative procedure for the synthesis of 3,4-dihydropyrano[c]chromenes

A mixture of aldehyde (10 mmol), malononitrile (10 mmol), 4-hydroxycoumarin (10 mmol) and 3.03 mol% ionic liquid was thoroughly mixed in a mortar followed by grinding for an appropriate time period till the completion of reaction as indicated by TLC (Table 2). After completion of the reaction, water was added and the mixture was filtered to separate the ionic liquid. Water was evaporated under reduced pressure to recover the ionic liquid which was reused to perform the subsequent model reaction. For the purification of the product, the precipitates were washed with cold aqueous ethanol and recrystallized from ethanol to give the pure product.

2.4. Spectral data for selected compounds

2.4.1. 2-Amino-4-phenyl-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (4a)

IR (KBr) ν: 3376 (NH_2), 2195 (CN), 1703 (C═O) cm^{-1}; ^{1}H NMR (*d*6-DMSO, 400 MHz) δ: 4.46 (s, 1H, CH), 7.23–7.91

Table 2 Synthesis of 3,4-dihydropyrano[c]chromenes in the presence of 3.03 mol% [DBU][Ac].

Entry	R	Time (min)	Yield[b] (%)	MP (°C) (observed)	MP (°C) (reported)
4a	C_6H_5	2	94	257–259	256–258 (Mehrabi and Abusaidi, 2010)
4b	4-$NO_2C_6H_4$	3	92	260–261	258–260 (Mehrabi and Abusaidi, 2010)
4c	3-NO_2 C_6H_4	4	91	256–258	258–260 (Mehrabi and Abusaidi, 2010)
4d	4-Cl C_6H_4	3	93	259–260	256–258 (Mehrabi and Abusaidi, 2010)
4e	4-F C_6H_4	3	95	258–259	260–262 (Mehrabi and Abusaidi, 2010)
4f	3,4-$(OCH_3)_2$ C_6H_3	7	89	227–229	228–230 (Mehrabi and Abusaidi, 2010)
4g	2-Cl C_6H_4	3	93	245–246	245–247 (Shaabani et al., 2005)
4h	4-$OCH_3C_6H_4$	10	93	240–242	238–240 (Mehrabi and Abusaidi, 2010)
4i	4-$(CH3)_2NC_6H_4$	13	91	265–266	265–267 (Mehrabi and Abusaidi, 2010)
4j	4-$CH_3C_6H_4$	5	91	253–255	251–253 (Mehrabi and Abusaidi, 2010)
4k	2-furyl	2	92	250–251	250–252 (Khurana et al., 2010)

Reaction Conditions: Aldehyde: 4-hydroxycoumarin: malononitrile in 1:1:1 (molar ratio) grinding at room temperature in the presence of ionic liquid [DBU][Ac] (3.03 mol%).

[a] Isolated yield.