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Amberlyst A-21®: An efficient, cost-effective and recyclable catalyst for the synthesis of substituted 4*H*-chromenes

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Abstract

A variety of substituted 4*H*-chromene derivatives have been synthesized in good to excellent yields from *o*-hydroxybenzaldehydes and ethyl cyanoacetate or malononitrile in ethanol using inexpensive and reusable catalyst i.e., Amberlyst A-21® under mild reaction conditions. The recovered activated catalyst is recycled in five times subsequent runs with no decrease in activity. The use of reusable catalyst makes this procedure quite simple, more convenient, economically viable and environmentally friendly.

Keywords: *o*-Hydroxybenzaldehyde; Heterogeneous catalysis; Ethyl cyanoacetate; Chromenes

2*H*-1-Benzopyrans (2*H*-chromenes) and 3,4-dihydro-2*H*-1-benzopyrans (chromans) have attracted much synthetic interest because of the biological activity of their naturally occurring representatives [1,2]. In addition, 2-aminochromenes and their derivatives are known to exhibit a wide spectrum of biological activities including anti-hypertensive and anti-ischemic behavior [3–5]. Substituted 4*H*-chromenes are particularly versatile compounds that bind Bcl-2 protein and induce apoptosis in tumor cells. Specifically, Bcl-2 can contribute to neoplastic cell expansion by preventing normal cell turnover caused by physiological cell death mechanisms. High levels of the Bcl-2 gene expressions are found in a wide variety of human cancers and can lead to tumor cell resistance to conventional chemotherapy and radiotherapy. Thus, Bcl-2 protein binding compounds provide a promising lead for the development of potential anti-cancer agents and direct methods for their synthesis are highly desirable [6–8]. However, no attempt has been made to recycle the catalyst, thereby making the process more economic and environment-friendly. In recent years, the use of heterogeneous catalysts such as ion-exchange resins, clays and zeolites has received great attention in different areas of organic synthesis [9–11] because of their simplicity in operation, environmental compatibility, reusability, greater selectivity, non-corrosiveness and ready availability of the reagents at low cost. Particularly, ion-exchange resins make the reaction processes quite simple, more convenient, economic and environmentally benign which enable them to function as efficient catalysts for various transformations [12–14]. Amberlyst-21® is a bead form, weak base ion-exchange resin developed for removal of acidic materials from non-aqueous solutions. It is supplied in the water-moist free base form. Amberlyst-21® was purchased from Sigma–Aldrich and was used as such without any further purification. A macro-reticular sulfonic acid-based polystyrene anion exchange resin, Amberlyst-21® is an inexpensive and commercially available solid basic catalyst, which is very familiar for various organic transformations [15–19]. The catalyst's characteristics are presented in Table 1.

In this report, we wish to report a simple and efficient protocol for the synthesis of 4*H*-chromenes using a cheap and reusable ion-exchange resin, i.e., Amberlyst A-21®. Accordingly, treatment of *o*-hydroxybenzaldehyde with ethyl cyanoacetate in the presence of Amberlyst A-21® in ethanol at ambient temperature gave the corresponding 2-amino-4*H*-chromene derivative **3a** in 85% yield (Scheme 1).

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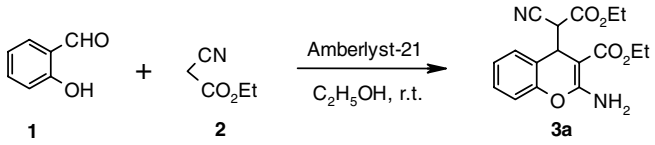
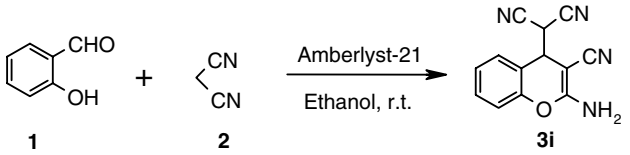
Table 1
Properties of Amberlyst A-21® catalyst

Resin	Anion-exchange resin
Nature	Weakly basic with active group
Form	Macro-reticular
Surface area	25 $m^2 g^{-1}$
Porosity	47%
Particle size	356–1000 *v*m
moister content	57%
Maximum temperature	383–393 K
Ion-exchange capacity g	4.8 meq g^{-1} or 1.3 meq ml^{-1}



Scheme 1.

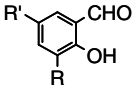
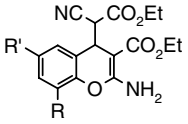
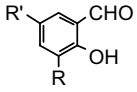
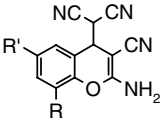
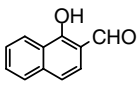
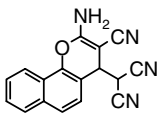


Scheme 2.

Encouraged by the results obtained with *o*-hydroxybenzaldehyde, we turned our attention to various substituted salicylaldehydes. Interestingly, several substituted *o*-hydroxybenzaldehydes underwent smooth coupling with ethyl cyanoacetate to furnish the respective 4*H*-chromene derivatives in high yields (entries **a**–**h**, Table 2). However, treatment of *o*-hydroxybenzaldehyde with malononitrile under similar conditions gave the corresponding 4*H*-chromene derivative **3i** in good yield with high diastereoselectivity (Scheme 2).

Only a single diastereomer was obtained in the reaction of malononitrile with *o*-hydroxybenzaldehydes, whereas,

Table 2
Preparation of 4*H*-chromene derivatives using Amberlyst A-21®

Entry	*o*-Hydroxy aldehyde **1**	Substrate **2**	Product[a] **3**	Diastereoisomeric ratio[b]		Time (h)	Yield (%)[c]
							
a	R=R′=H	$NCCH_2COOEt$	R=R′=H	**3a**	4:1	4.0	85
b	R=H; R′=Br	$NCCH_2COOEt$	R=H; R′=Br	**3b**	5:1	2.0	88
c	R=Br; R′=Br	$NCCH_2COOEt$	R=Br; R′=Br	**3c**	5:1	3.0	81
d	R=NO_2R′=MeO	$NCCH_2COOEt$	R=NO_2R′=MeO	**3d**	6:1	2.0	92
e	R=H; R′=NO_2	$NCCH_2COOEt$	R=H; R′=NO_2	**3e**	4:1	3.0	94
f	R=NO_2; R′=H	$NCCH_2COOEt$	R=NO_2; R′=H	**3f**	4:1	3.0	87
g	R=Cl; R′=H	$NCCH_2COOEt$	R=Cl; R′=H	**3g**	5:2	3.5	68
h	R=MeO; R′=H	$NCCH_2COOEt$	R=Cl; R′=H	**3h**	5:1	5.0	73
							
i	R=R′=H	$NCCH_2CN$	R=R′=H	**3i**		4.0	70
j	R=R′=Br	$NCCH_2CN$	R=R′=Br	**3j**		2.0	75
k	R=Br; R′=Br	$NCCH_2CN$	R=Br; R′=Br	**3k**		3.0	80
l	R=NO_2; R′=MeO	$NCCH_2CN$	R=NO_2; R′=MeO	**3l**		2.0	91
m	R=H; R′=NO_2	$NCCH_2CN$	R=H; R′=NO_2	**3m**		3.0	89
n	R=NO_2; R′=H	$NCCH_2CN$	R=NO_2; R′=H	**3n**		3.0	89
o	R=MeO; R′=H	$NCCH_2CN$	R=MeO; R′=H	**3o**		6.0	69
p		$NCCH_2CN$		**3p**		6.0	71

[a] All product were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Diastereomeric ratio was confirmed by ^1H NMR spectrum of a crude product.
[c] Isolated and unoptimized yields.