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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

Catalysis by Amberlyst A-21: A Greener Approach to 4,5,6,7-Tetrahydro-1Hindazol-3(2H)-ones via Construction of Cyclohexanones

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Accepted author version posted online: 08 Nov 2013. Published online: 19 Mar 2014.

To cite this article: Manam Sreenivasa Rao , Meda Haritha , Sunder Kumar Kolli , Mandava V. Basaveswara Rao & Manojit Pal (2014) Catalysis by Amberlyst A-21: A Greener Approach to 4,5,6,7-Tetrahydro-1H-indazol-3(2H)-ones via Construction of Cyclohexanones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:8, 1076-1083, DOI: 10.1080/00397911.2013.844260

To link to this article: <u>http://dx.doi.org/10.1080/00397911.2013.844260</u>

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Synthetic Communications[®], 44: 1076–1083, 2014 Copyright © Taylor & Francis Group, LLC ISSN: 0039-7911 print/1532-2432 online DOI: 10.1080/00397911.2013.844260

CATALYSIS BY AMBERLYST A-21: A GREENER APPROACH TO 4,5,6,7-TETRAHYDRO-1H-INDAZOL-3(2*H*)-ONES VIA CONSTRUCTION OF CYCLOHEXANONES

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GRAPHICAL ABSTRACT



Abstract The 4,5,6,7-tetrahydro-1H-indazol-3(2H)-one derivatives have been synthesized in good yields via a two-step method in a single pot. The initial step involved the construction of cyclohexanone ring from aromatic aldehydes and β -ketoester in i-PrOH using an inexpensive and reusable catalyst (i.e., Amberlyst A-21) under mild reaction conditions. The utility of this catalyst has been demonstrated in synthesizing a range of cyclohexanone derivatives. The catalyst can be recovered and recycled, which makes this procedure simple, convenient, economically viable, and environmental friendly.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications[®] for the following free supplemental resource(s): Full experimental and spectral details.]

Keywords Amberlyst A-21; catalysis; cyclohexanone; indazole

Received July 19, 2013.

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INTRODUCTION

The development of methodologies that involve the use of inexpensive and reusable catalysts under mild and environmentally friendly reaction conditions is one of the major goals in green and sustainable chemistry. Methodologies leading to various carbocyclic/heterocyclic structures are in high demand for both academic and industrial applications.

The 4,5,6,7-tetrahydro-1H-indazole framework (A, Fig. 1) has attracted considerable interest in the area of medicinal chemistry and drug discovery because of its promising pharmacological properties (e.g., antitumor,^[1] antimicrobial,^[2] nitric oxide synthase inhibitory,^[3] dopaminergic,^[4] HMG-CoA reductase inhibitory,^[5] cholesterol lowering,^[6] mitotic motor protein modulatory,^[7] and Rho-kinase inhibitory^[8] activities). Additionally, evaluation of a series of 1-aryl-4,5,6,7-tetrahydro-1H-indazole-5-carboxylic acidsfor their anti-inflammatory activities led to the identification of 1-phenyl-4,5,6,7tetrahydro-1*H*-indazole-5-carboxylic acid (**B**, Fig. 1) that showed high activities in vivo with ED₅₀ value of 3.5 mg/kg in the carrageenan edema test,^[9] Similarly, 2-methyl-3-methylamino-4,5,6,7-tetrahydroindazole (C, Fig. 1) has showed anti-inflammatory and analgesic activities.^[10] Notably, compared to A its derivative D, 4,5,6,7-tetrahydro-1H-indazol-3(2H)-one (Fig. 1), has not been explored for the identification of biologically active new chemical entities (NCE). These observations and our interest in 4,5,6,7-tetrahydro-1*H*-indazol-3(2*H*)-ones prompted us to devote our efforts toward the generation of small molecules based on scaffold **D**. Herein, we report our results on the synthesis of these drug-like molecules via a two-step method in a single pot (Scheme 1).

RESULTS AND DISCUSSION

Our strategy was based on the construction of the cyclohexanone ring under clean conditions followed by the formation of fused indazole ring. We explored the use of Amberlyst A-21 as an inexpensive and readily available catalyst for the first step. The resin-bound (or heterogeneous) catalysts are gaining increased interest among modern organic chemists as the use of homogenous catalysts often involved their cumbersome separation from the products and subsequent disposal as well as toxicities. Additionally, resin-bound catalysts are easy to handle and recover and also provide enhanced safety for potentially explosive reagents. Amberlyst A-21 is a weakly basic, macroreticular



Figure 1. 4,5,6,7-Tetrahydro-1H-indazole and its bioactive derivatives.



Scheme 1. Generation of a library of small molecules based on scaffold D.

ion-exchange resin with alkyl amine functionality (it is bonded to the macroreticular structure of ion exchange resin). We performed a systematic study on the reaction of 4-bromobenzaldehyde (1a) and ethyl acetoacetate (2a) in the presence of Amberlyst A-21 under various conditions (Table 1). While the use of macroreticular weak base polymeric catalyst (Amberlyst A-21) in various chemical transformations has been reported in the literature.^[11–15] its use in the construction of cyclohexanone ring has not been explored extensively earlier. On the other hand synthesis of cyclohexanone 3 has been carried out earlier via the condensation of an aldehyde with β -keto esters or 1,3-diketone in the presence of a base such as piperidine,^[16,17] pyrrolidine,^[18] and morpholine^[19] or a strong base (e.g., NaOMe).^[20] The Amberlyst A-21-mediated reaction of **1a** with **2a** was carried out initially in *i*-PrOH at 80 °C in the presence of 5% w/w catalyst (entry 1, Table 1) when the desired product 3a was isolated only in 23% yield after 15h. Though the increase in catalyst loading increased the product yield significantly (entries 2 and 3, Table 1) the best result was obtained when 20% w/w Amberlyst A-21 was used (entry 4, Table 1). The product **3a** was isolated in 90% yield in this case and was obtained by filtering the reaction mixture followed by washing the solid resin with warm *i*-PrOH (55–60 °C) (to elute all the organic compounds from the resin) and then reducing the volume of combined filtrate via evaporation to give the crystalline product on cooling. Notably, further increase in catalyst loading did not improve the yield of **3a** (entry 5, Table 1). Similarly, the increase in reaction temperature or time did not improve the product yield. The use of other solvents [e.g., 1,4-dioxane, tetrahydrofuran (THF), dimethylformamide (DMF), toluene, EtOAc, and MeCN] was also

	OHC-Br +	OEt Ambe	rlyst A-21 blvent heat HO	Break
Entr	Amount y (w/w)	Solvent	T (°C); t (h)	Yield $(\%)^b$
1	5%	<i>i</i> -PrOH	80; 15	23
2	10%	<i>i</i> -PrOH	80; 15	45
3	15%	<i>i</i> -PrOH	80; 15	67
4	20%	<i>i</i> -PrOH	80; 15	90 (85, 83, 80) ^c
5	25%	<i>i</i> -PrOH	80; 15	87
6	20%	1,4-Dioxane	80; 15	65
7	20%	THF	65; 24	30
8	20%	DMF	100; 24	43
9	20%	Toluene	110; 24	56
10	20%	EtOAc	80; 24	30
11	20%	MeCN	80; 24	19

 Table 1. Amberlyst A-21-mediated reaction of 1a with $2a^a$

^{*a*}All the reactions were carried out by using 4-bromo benzaldehyde (1a), ethyl acetoacetate (2a), and Amberlyst A-21 in a solvent (10 mL) under open air. ^{*b*}Isolated yields.

Catalyst was reused for additional three runs and figures within parentheses indicate the corresponding yield for each run.

examined but they were found to be less effective (entries 6–11, Table 1). While the reasons for these observations are not clearly understood, it is known that the reactivity of polystyrene resin is mainly governed by the accessibility of the reactants to the catalytic sites via swelling of the resin in solvents. It seemed that the swelling of resin perhaps was more effective in *i*-PrOH than any other solvents tested. The recyclability of the catalyst was examined by recovering it via filtration, washing with *i*-PrOH and THF, and reusing it for an additional three runs in the reaction of **1a** with **2a**. The product **3a** was isolated without significant loss of its yield in these cases (entry 4, Table 1). Moreover, these reactions were performed under open air and therefore do not require the use of an inert or anhydrous atmosphere. Nevertheless, the use of Amberlyst A-21 (20% w/w) in *i*-PrOH at 80 °C was identified as the optimum reaction conditions for the synthesis of **3a**.

With the optimized reaction conditions for the preparation of cyclohexanone derivative in hand, we then focused on the direct and efficient synthesis of 4,5,6,7-tetrahydro-1*H*-indazol-3(2*H*)-ones. Thus, the diethyl-2-(4-bromophenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3a) generated in situ via the reaction of 1a with 2a was treated with hydrazine hydrate 4 in the same pot at 80 °C for 12h when the corresponding indazole derivative 5a was isolated in good yield (Scheme 2). The reaction proceeded well under this condition and after completion of the reaction (confirmed by thin-layer chromatography, TLC) the resin was separated by filtration. The filtrate was concentrated under low vacuum to give the crude product, which was purified by recrystallization from ethanol without any column chromatography. This allowed us to prepare other indazoles, 6-hydroxy-6-methyl-4-(4-nitrophenyl)-5-propionyl-4,5,6,7-tetrahydro-1*H*-indazol-3(2*H*)-one (5b) and 4-(6-hydroxy-6-methyl-3-oxo-5-propionyl-2,3,4,5,6,7-hexahydro-1H-indazol-4-yl) benzonitrile (5c), following the same strategy (Scheme 2). Both 5b and 5c were isolated in good yield, highlighting the utility of this method. It is worth mentioning that worldwide initiatives against environmental pollution have forced synthetic chemists to opt for the solvents that are more ecofriendly. Because the organic solvents are considered the greatest contributors toward environmental waste, the use of environmentally compatible solvents, such as water or *i*-PrOH, is highly desirable. Thus the present *i*-PrOH-based strategy represents a greener approach toward 4,5,6,7-tetrahydro-1H-indazol-3(2H)-ones in



Scheme 2. One-pot synthesis of 4-(4-bromophenyl)-6-hydroxy-6-methyl-5-propionyl-4,5,6,7-tetrahydro-1*H*-indazol-3(2*H*)-one (**5a**), 6-hydroxy-6-methyl-4-(4-nitrophenyl)-5-propionyl-4,5,6,7-tetrahydro-1*H*-indazol-3(2*H*)-one (**5b**), and 4-(6-hydroxy-6-methyl-3-oxo-5-propionyl-2,3,4,5,6,7-hexahydro-1*H*-indazol-4-yl) benzonitrile (**5c**).



Figure 2. Examples of cyclohexanone derivatives 3 (with yield) synthesized using Amberlyst A-21-mediated reaction.

a single pot. Because all these reactions were performed under open air, the methodology is free from the risk of pressure development, often observed in reactions performed in isolated vessels. The methodology therefore is amenable for scale-up.

To demonstrate the generality and scope of the Amberlyst A-21-mediated synthesis of cyclohexanones we prepared several other derivatives as shown in Fig. 2 using a range of aldehydes 1. Thus 1 was reacted with ethyl acetoacetate (2a) in the presence of Amberlyst A-21 in *i*-PrOH at 80 °C for 15h under open air. The desired products 3 were isolated in good yields irrespective of the nature and type of aldehydes (e.g., aryl, heteroaryl, or alkyl aldehydes) employed. Once again the potential utility of these compounds was demonstrated by converting the two representative compounds 3d and 3f to the corresponding 4,5,6,7-tetrahydro-1*H*-indazol-3(2*H*)-ones separately via the reaction with hydrazine (Scheme 3). However, the reaction of 3e with hydrazine was not clean, perhaps due to the presence of reactive aldehyde moiety as an additional functional group.



Scheme 3. Synthesis of ethyl 6-hydroxy-6-methyl-3-oxo-4-p-tolyl-2,3,4,5,6,7-hexahydro-1H-indazole-5-carboxylate (5d) and ethyl 4-(4-chlorophenyl)-6-hydroxy-6-methyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazole-5-carboxylate (5f).



Scheme 4. Proposed reaction mechanism.

Based on the fact that Amberlyst A-21 is a weakly basic, macroreticular resin with alkyl amine functionality, a plausible mechanism for the present two-step method in a single pot is shown in Scheme 4. The reaction seemed to proceed via a Knoevenagel condensation of 1 with 2 in the initial step. The resin facilitates the generation of carbanion E-1 from 2 possessing an active methylene group. The reaction of E-1 with the aldehyde 1 affords the Knoevenagel product (E-2), which on Michael type addition by the carbanion E-1 affords E-3. An intramolecular aldol type condensation of E-3 mediated by the resin provides the cyclohexanone derivatives 3. The reaction of hydrazine 4 with 3 in the same pot affords the 4,5,6,7-tetrahydro-1*H*-indazol-3(2*H*)-one derivatives (5).

CONCLUSIONS

In conclusion, 4,5,6,7-tetrahydro-1*H*-indazol-3(2*H*)-one derivatives have been synthesized in good yields via a two-step method in a single pot. The initial step involved the construction of cyclohexanone ring from aromatic aldehydes and β -ketoester in *i*-PrOH using inexpensive and reusable catalyst (i.e., Amberlyst A-21) under mild reaction conditions. The utility of this catalyst has been demonstrated in synthesizing a range of cyclohexanone derivatives. The catalyst can be recovered and recycled, which makes this procedure simple, convenient, economically viable, and environmentally friendly. The present Amberlyst A-21–catalyzed method therefore has potential for the generation of library of small molecules useful for synthetic and medicinal applications.

EXPERIMENTAL

Preparation of Diethyl 4'-Bromo-5-methyl-3-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2,6-dicarboxylate (3a)

Amberlyst A-21 (20% w/w) was added to a solution of ethyl acetoacetate 2a (2.2 mmol) and 4-bromobenzaldehyde 1a (1.0 mmol) in *i*-PrOH (10 ml) and the mixture was stirred at 80 °C for 15h. After completion of the reaction as indicated by

thin-layer chromatography, (TLC), the mixture was cooled to room temperature. The resin was separated by filtration and washed with warm *i*-PrOH (55–60 °C) to elute all the contaminated organic compounds from the resin. The combined filtrate was concentrated under low vacuum to reduce its volume and then cooled to give the desired product **3a** as a white solid; mp 150–151 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.48 (d, *J*=8.0 Hz, 2H), 7.27 (d, *J*=8.0 Hz, 2H), 4.97 (s, OH), 3.97–3.79 (m, 6H), 3.29 (d, *J*=8.0 Hz, 1H), 2.92 (d, *J*=16.0 Hz, 1H), 2.34 (d, *J*=16.0 Hz, 1H), 0.96 (s, 3H), 0.88 (t, *J*=8.0 Hz, 3H), 0.87 (t, *J*=8.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 200.7, 173.5, 167.4, 137.3, 131.7, 129.7, 121.6, 72.9, 62.2, 61.1, 60.9, 56.7, 52.6, 44.5, 28.5, 13.9, 13.6; IR (KBr): 3433, 1736, 1598, 1364, 1174, 775 cm⁻¹; HRMS (ESI): calcd. for C₁₉H₂₄O₆Br (M+H)⁺ 427.0756; found 427.0736; MS (ESI): *m/z* ([M+H]⁺): 427.1

General Procedure for the Preparation of Compounds 5a-c

Amberlyst A-21 (20% w/w) was added to a solution of ethyl acetoacetate **2a** (2.2 mmol) and aldehyde **1** (1.0 mmol) in ethanol (10 ml), and the mixture was stirred at 80 °C for 15 h to ensure the completion of the reaction (monitored by TLC). The reaction mass was cooled to room temperature, and hydrazine hydrate **4** (1.0 mmol) was added. The mixture was stirred at 80 °C for another 12 h. After completion of the reaction (confirmed by TLC) the resin was separated by filtration. The filtrate was concentrated under low vacuum to give the crude product, which was purified by recrystallization from ethanol to afford the pure product **5a–c**.

Recovery of the Catalyst

The recovered Amberlyst A-21 resin, obtained by filtering off the reaction product, was washed successively with THF (5 mL) and EtOH (5 mL) three times and dried at 100 °C for 2 h. The efficiency of the catalyst was not changed significantly after using it three additional times in the model reaction, shown in Table 1.

ACKNOWLEDGMENT

The authors thank the management of Dr. Reddy's Institute of Life Sciences for continuous support and encouragement.

SUPPORTING INFORMATION

Full experimental details, and spectral data can be found via the Supplementary Content section of this article's Web page.

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