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Facile imine synthesis under green conditions using Amberlyst® 15

Giovanna Bosica [Corresp., 1] , **Roderick Abdilla** [1] , **Kaylie Demanuele** [1] , **Josef Fiteni** [1]

[1] Department of Chemistry, University of Malta, Msida, Malta

Corresponding Author: Giovanna Bosica
Email address: giovanna.bosica@um.edu.mt

Imines and their derivatives are of great interest to organic synthetic chemists due to their involvement as key intermediates which facilitate the construction of nitrogen heterocycles, particularly the formation of alkaloids. Imine formation by condensation of primary amines with aliphatic and aromatic aldehydes and cyclohexanone has been investigated under environmentally-friendly solventless heterogeneous catalysis. An array of different imines was obtained in excellent yields in appreciably short reaction times using Amberlyst® 15 as a heterogeneous catalyst. The latter was used owing to its high commercial availability, recyclability, ease of separation from reaction mixture and versatility.

1 Facile imine synthesis under green conditions using
2 Amberlyst® 15

4 Giovanna Bosica*, Roderick Abdilla, Kaylie Demanuele, Josef Fiteni

6 Department of Chemistry, Green Synthetic Organic Chemistry Laboratory, University of Malta, Msida,
7 MSD 2080, Malta.

9 E-mail: giovanna.bosica@um.edu.mt

11 Abstract

12 Imines and their derivatives are of great interest to organic synthetic chemists due to their
13 involvement as key intermediates which facilitate the construction of nitrogen heterocycles,
14 particularly the formation of alkaloids. Imine formation by condensation of primary amines with
15 aliphatic and aromatic aldehydes and cyclohexanone has been investigated under
16 environmentally-friendly solventless heterogeneous catalysis. An array of different imines was
17 obtained in excellent yields in appreciably short reaction times using Amberlyst® 15 as a
18 heterogeneous catalyst. The latter was used owing to its high commercial availability,
19 recyclability, ease of separation from reaction mixture and versatility.

21 Keywords
22 Solventless; Amberlyst® 15; Imine synthesis; Heterogeneous catalysis; Aryl/alkyl amines, Easy
23 separation

25 1. Introduction

26 Imines are fundamental intermediates in the synthesis of N-containing organic molecules which
27 are biologically active (particularly alkaloids) or used in various industrial procedures.[1] Their
28 formation via the condensation of amines with aldehydes or ketones is a reversible process.[1] In
29 fact, the use of imines as intermediates in multicomponent reactions is very ubiquitous due to the
30 same equilibrium which exists.[2] Imine-based multicomponent reactions which have gained
31 considerable attention in the past few years include: formation of quinolizidines and
32 indolizidines via A[3]coupling, other Mannich-type reactions (nitro-Mannich, aza-Friedel-Crafts,
33 Petasis), and the intramolecular aza-Diels-Alder reaction.[3,4,5]
34 In order to be able to drive the condensation process to completion, the classical method required
35 azeotropic distillation by a Dean-Stark apparatus which obviously necessitated the use of excess
36 amounts of solvents.[6] Subsequently, alternative eco-friendly procedures were developed
37 including the Schmidt reaction, the oxidative-dehydrogenation of amines and the oxidative
38 coupling of alcohols and amines just to name a few.[7] Such procedures still may suffer from one
39 or more of the following disadvantages: require expensive metallic catalysts, have a lower atom

40 economy, require long reaction times, require the use of toxic solvents and show overall low
41 environmental benignity.
42 After the incorporation of the green chemistry principles into the synthetic chemistry modus
43 operandi, following the works of Anastas and Werner, the above mentioned syntheses were
44 improved further and rendered more eco-friendly through the use of heterogeneous catalysts such
45 as: sulfated-TiO_2, montmorillonite K-10 clay, sulfated nano-ordered silica and zeolites.[8,9,10,11]
46 Further recently developed sustainable methodologies have been reported using irradiation
47 techniques.[12] Moreover the addition of dehydrating agents such as phosphorous-pentoxide-silica
48 have also been shown to drive the reaction to completion by removing the condensation product,
49 ergo water.[13] Obviously such agents require oven drying and reactivation for future re-use.
50 Another difficulty associated with this synthetic reaction is that in general, ketones are much less
51 reactive when compared with aldehydes rendering ketimine synthesis even more unfavourable
52 and non-green.
53 In the following research, in continuation of our interest in the application of heterogeneous
54 catalysts,[14] herein we report how various heterogeneous catalysts and some desiccants were tried
55 and compared in terms of activity and efficiency for the imine synthesis reaction. Amberlyst®
56 15, a cheap commercially available catalyst is found to give the highest yields in short reaction
57 times under neat conditions. In addendum, the unprecedented synthesis of the ketimine from the
58 condensation of cyclohexanamine and cyclohexanone proved successful.
59

60 ## 2. Results and discussion

61 During the initial screening, the reaction between benzaldehyde (**1a**) and *t*-butylamine (**2a**) was
62 chosen as the model reaction (**Scheme 1**). The latter was always performed at room temperature
63 under quasi-solvent-free conditions in the presence/absence of a number of heterogeneous
64 catalysts and desiccants. In addition, the molar ratios of the reagents and catalyst quantities were
65 also varied. **Tables 1-2** show the results of the preliminary catalyst/drying agent screening trials.
66

67 **Scheme 1.**
68

69 **Table 1.**
70

71 **Table 2.**
72

73 As evidenced, out of the catalysts and desiccants tried and tested, the best yields were obtained
74 using Montmorillonite K-10, Amberlyst® 15 and acidic alumina. However, the work up of the
75 reactions involving either MK-10 or acidic alumina required the addition of more solvent than
76 that involving Amberlyst® 15 owing to their physical state (powder). Henceforth, Amberlyst®
77 15 (being in the form of beads) was selected for the subsequent optimization trials especially
78 considering its ease of separation from the reaction mixture. In addition, it was discovered that a
79 smaller amount of Amberlyst® 15 could result in even higher yields (**Table 3**) possibly owing to
80 easier mechanical stirring and less product adsorption onto the catalyst beads.
81

82 **Table 3.**
83

84 One of the main limitations of the condensation of primary amines and aldehydes/ketones is the
85 equilibrium which exists between the products and the substrates. This explains why in the initial
86 trials the amine was used in excess, ergo, to shift the equilibrium forward. Yet, as outlined in
87 **Table 4,** the yields remained practically the same even when the latter mentioned excess was
88 decreased to 0.1 equivalents only.
89

90 **Table 4.**
91

92 Subsequently, having identified the ideal conditions (neat, room temperature, 0.2 g per 5 mmol
93 Amberlyst® 15, 0.1 equivalent excess of amine), the substrate scope could be expanded by
94 varying the aldehydes and the amines. In general, the best outcomes were obtained (
95 **Table** 5) when using aromatic aldehydes and aliphatic primary amines due to the higher
96 reactivity of the aldehydes as opposed to ketones and the greater nucleophilic character of
97 aliphatic amine as opposed to aromatic amines.
98

99 **Table 5.**
100

101 Positively, despite their inherent lack of reactivity, aromatic amines also gave appreciable yields
102 as outlined in
103 **Table** 6. Not only, but the cyclic aliphatic amine, c-hexylamine, was able to react successfully
104 with the cyclic ketone, cyclohexanone (**Scheme 1**) to give the product (**3s**) in 85% yield.
105

106 **Table 6.**
107

108 **Scheme 1.**
109

110 Lastly, the catalyst exhibited good recyclability because the model reaction could be repeated up
111 to 5 times with the same catalyst with the yield decreasing by 10% between the first and last trial

112 (**Figure 1**). The latter decrease is most probably a result of sulfonic acid group inactivation by
113 the reaction with the amine reactant.

114
115 **Figure 1.**

116

3. Conclusions

118 The heterogeneous, safe-to-handle, relatively-cheap and commercially-available Amberlyst® 15
119 was found to be the ideal catalyst for the synthesis of various imines using both aliphatic and
120 aromatic amines and aldehydes (72 – 99% yields, 17 examples) in significantly short reaction
121 times (2 – 4 hours) at room temperature in neat conditions. The catalyst's physical state, i.e.
122 being in the form of microporous beads, enabled it to be easily recovered with minimal solvent
123 use during work up and reused for up to 5 times.

124

4. Experimental

4.1. Materials used

127 All commercially available chemicals were purchased from Aldrich and used without further
128 purification.

129

4.2. Instrumentation

131 For the identification of the reaction mixture components and monitoring of the reactions, a
132 Shimadzu GC-2010® instrument was utilised. A HiCap5 column 30 m in length, having an
133 internal diameter of 0.32 mm and with a particle size of 0.25 μm, was adopted as the stationary
134 phase of chromatography. The carrier gas used as the mobile phase of the chromatography
135 process was nitrogen, N_2.
136 IR spectra were recorded on a Shimadzu IRAffinity-1 FTIR spectrometer calibrated against a
137 1602 cm^{-1} polystyrene absorbance spectrum. Samples were analysed as KBr pellets or as thin-
138 films in between sodium chloride discs.
139 The ^1H NMR spectra were recorded on a Bruker Avance III HD® NMR spectrometer, equipped
140 with an Ascend 500 11.75 Tesla superconducting magnet (operating at 500.13 MHz for ^1H) and
141 a multinuclear 5 mm PABBO probe. Samples were dissolved in deuterated chloroform (with
142 TMS).
143 Mass spectra were usually performed via the direct-infusion method using a Waters®
144 ACQUITY® TQD system with a tandem quadrupole mass spectrometer after dissolving the
145 samples in ethyl acetate.

146

4.3. General procedure

148 The general procedure for the imine-synthesis reaction involved stirring the aldehyde (5 mmol)
149 and the amine (5.5 mmol) in the presence of 0.2 g of A15 catalyst under neat conditions at room
150 temperature in a nitrogen-dried 25 mL one-neck round bottomed flask. The reaction was
151 monitored via both TLCs and/or GC analysis. The catalyst was filtered off by suction and

152 washed appropriately with diethyl ether solvent. The filtrate was concentrated by rotary
153 evaporation and by a double-stage vacuum oil pump in order to remove the unreacted amine for
154 reactions involving low-boiling amines. The products of aromatic amines were purified by
155 recrystallization from ethanol or by column chromatography using a 9:1, 8:2 or 7:3 hexane/ethyl
156 acetate eluant ratio. The TLC plates used for monitoring were composed of silica on PET with
157 fluorescent indicator. Plates were observed under a UV lamp at a wavelength of 254 nm before
158 staining in an iodine-saturated chamber. Analytical data for all products are reported in the
159 Supporting Information File.
160

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Trials involving a number of readily available desiccants

1   **Table 1. Trials involving a number of readily available desiccants**

Entry[a]	Desiccant	Reaction time (h)	Yield[b] 3a (%)
1a[c]	N/A	9.5	81
1b	Anhydrous $MgSO_4$ 1(g)	8	88
1c	Molecular sieves $(3Å)^{[d]}$ (0.5 g)	6.5	98
1d	Molecular sieves $(4Å)^{[d]}$ (0.5 g)	4	94

2   a. All reactions were carried out under solventless conditions on a 5 mmol scale using a 1 : 3 molar ratio of 1a
3   : 2a
4   b. Yield of pure isolated product
5   c. No desiccant or catalyst added
6   d. Effective pore size in Angstrom
7

Optimization trials involving various heterogeneous catalysts

1 **Table 1. Optimization trials involving various heterogeneous catalysts**

Entry[a]	Catalyst (Amount in g)	Reaction time (h)	Yield[b] 3a (%)
2a	Amberlyst® A-21 (1.50)	2	78
2b	Amberlyst® 15 (1.50)	2	86
2c	Montmorillonite K-10 (0.30)[c]	2.5	95
2d	Nafion® SAC-13 (0.40)[d]	2	78
2e	Acidic alumina (1.25)	2	97
2f	Neutral alumina (1.25)	2.5	75
2g	Basic Alumina (1.25)	2	49
2h	KF on basic alumina (1.00)	2.0	79
2i[e]	CuI on Amberlyst® A-21 (0.05)	1.5	80[f]

2   a.   All reactions were carried out in the presence of 1 mL of diethyl ether on a 5 mmol scale using a 1 : 3
3   molar ratio of benzaldehyde : amine. The addition of diethyl ether was required because reaction mixture
4   soon thickened significantly after reaction initiation.
5   b.   Yield of pure isolated product unless otherwise indicated
6   c.   A smaller amount of MK-10 (compared to other catalysts) was used because on addition of larger amounts
7   of MK-10, reaction mixture dried up immediately and the addition of 1 mL of diethyl ether was not enough
8   to aid stirring.
9   d.   When a larger amount of catalyst was used the Nafion beads kept moving out of reaction mixture and
10   adhering to reactant flask walls.
11   e.   Reaction carried out under solventless conditions owing to the small amount of catalyst
12   f.   Copper iodide leaching was noted due to residual green colour in the crude reaction mixture following
13   catalyst filtration.

Optimization trials involving changing the amount of Amberlyst® 15

1 **Table 1. Optimization trials involving changing the amount of Amberlyst® 15**

Entry[a]	Quantity of Amberlyst® 15 (g)	Reaction time (h)	Yield[b] 3a (%)
3a	0.6	2	98
3b	0.4	2	99
3c	0.2	2	99
3d	0.1	2.5	99
3e	0.05	3	97

2   a.   All reactions were carried out under solventless conditions at room temperature on a 5 mmol scale using a
3   benzaldehyde : *tert*-butylamine molar ratio of 1: 3
4   b.   Yield of pure isolated product

Optimization trials involving varying the reagent ratios

1 **Table 1. Optimization trials involving varying the reagent ratios**

Entry[a]	Aldehyde : amine molar ratio	Reaction time (h)	Yield[b] 3a (%)
4a	1 : 2	2	99%
4b	1 : 1.5	2	99%
4c	1 : 1.1	2	99%

2   a.   All reactions carried out under solventless conditions at room temperature on a 5 mmol scale

3   b.   Yield of pure isolated product

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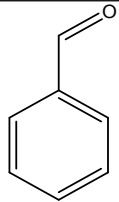
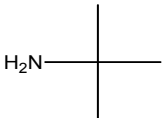
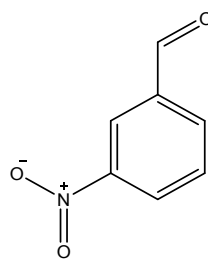
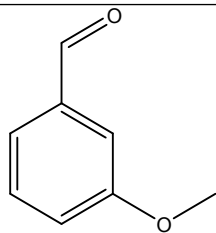
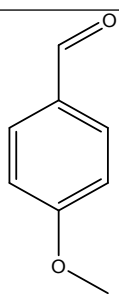
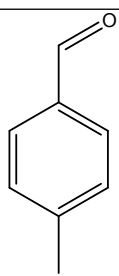
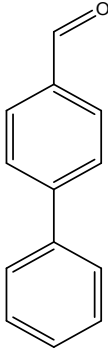
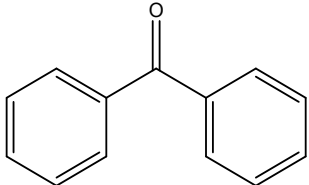
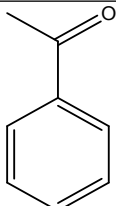
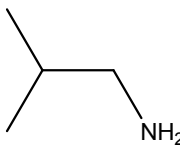
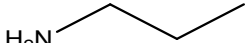
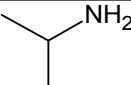
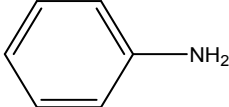
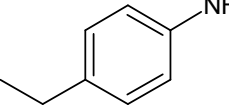

Condensation of primary aliphatic amines with aromatic aldehydes using Amberlyst®
15 as catalyst

1 **Table 1: Condensation of primary aliphatic amines with aromatic aldehydes using**
2 **Amberlyst® 15 as catalyst**

Entry[a]	Aldehyde/Ketone	Amine	Product	Time (h)	Yield (%)[b]
1	1a	2a	3a	2	99
2	1b	2a	3b	3	96
3	1c	2a	3c	4.5	93
4	1d	2a	3d	4.5	98
5	1e	2a	3e	3	97

6	1f	2a	3f	2	97
7ᶜ	1g	2a	3g	80	NYᵈ
8	1h	2a	3h	80	NYᵈ
9	1a	2b	3i	1	99
10	1b	2b	3j	1	97
11	1c	2b	3k	3	93
12	1d	2b	3l	2.5	92
13ᶜ	1a	2c	3m	1	98
14ᶜ	1a	2d	3n	1	99

3   a.   All reactions carried out under solventless conditions at RT using 0.2 g Amberlyst® 15 on a 5 mmol scale
4   using an amine equivalent excess of 0.1
5   b.   Yield of pure isolated product collected after work-up and purification

6   c.   Reactions carried out in a 1:1.5 aldehyde/ketone : amine molar ratio

7   d.   No pure product collected

Condensation of aromatic primary amines with aromatic aldehydes

1   **Table 1. Condensation of aromatic primary amines with aromatic aldehydes**

Entry[a]	Aldehyde	Amine	Product	Time (h)	Yield (%)[b]
1	1a	2e	3o	3	72
2	1b	2e	3p	2.5	81
3	1c	2e	3q	4	75
4[c]	1e	2f	3r	3	90

2   a. All reactions carried out under solventless conditions using 0.2 g Amberlyst® 15 on a 5 mmol scale using
3   an aldehyde/ketone : amine molar ratio of 1 : 1.1
4   b. Yield of pure isolated product collected by recrystallization from ethanol
5   c. Reactions carried out using a 1:1.5 aldehyde/ketone : amine ratio

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Figure 1

Amberlyst® 15 catalyst recycling trials for model reaction (to form product 3a)

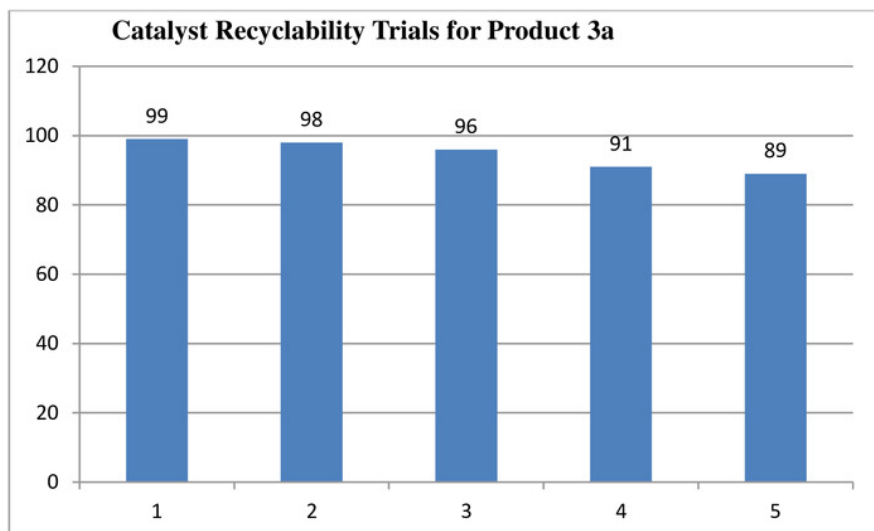
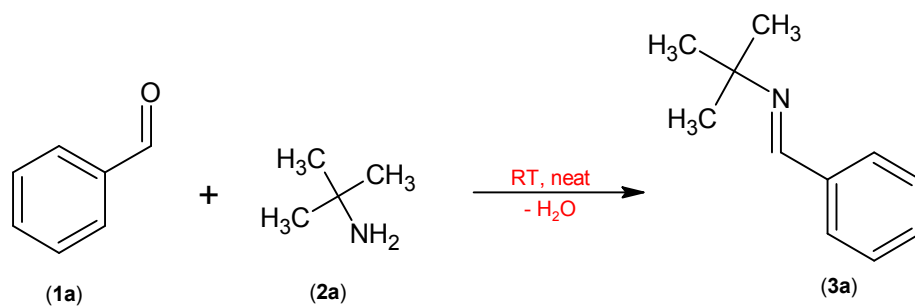
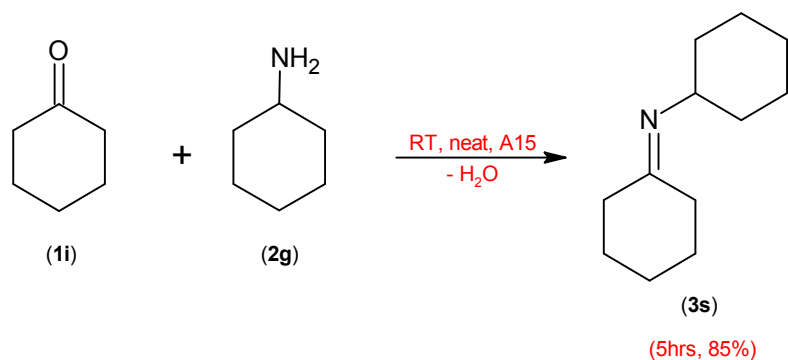



Figure 1. Amberlyst® 15 catalyst recycling trials for model reaction (to form product 3a)

3   **Scheme 1. Model reaction between benzaldehyde (1a) and *t*-butylamine (2a)**

(1i)   (2g)   RT, neat, A15
- H₂O

(3s)

(5hrs, 85%)

3   **Scheme 1. Condensation of cyclohexanamine (2g) with cyclohexanone (1i) in the presence**

4   **of Amberlyst® 15 catalyst at room temperature using an amine excess of 0.1 equivalent**