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# Organic synthesis in water: Green protocol for the synthesis of 2-amino furan derivatives

J.S. Yadav *, B.V. Subba Reddy, S. Shubashree, K. Sadashiv, D. Krishna Rao

*Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India*

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**Abstract**

Aldehyde, dimethyl acetylenedicarboxylate (DMAD) and cyclohexyl isocyanide undergo smooth coupling in water to produce the corresponding 2-aminofuran derivatives in good yields. Water helps to avoid the use of highly toxic and environmentally unfavorable solvents for this conversion.


*Keywords:* Water; Multi-component reaction; Furan derivatives

Recently, a great attention has been focused on the use of water as green solvent in various organic transformations. In addition to its abundance and for economical and safety reasons, water has naturally become as a substitute and an alternative environmentally benign solvent in organic synthesis [1]. The use of aqueous medium as solvent also reduces the harmful effects of organic solvents on the environment. This becomes further sophisticated if these reactions can be performed using inexpensive reagents. The use of ionic liquids as solvents has attracted much attention in the area of green synthesis. However, high cost of the conventional room temperature of ionic liquids and apprehension regarding the toxicity of some of them has led to the use of more benign alternatives [2]. Recently, water has been used as an environmentally benign solvent in a number of organic transformations. The art of performing multi-component coupling reactions in a one-pot operation has received considerable interest due to their ability to generate molecular diversity and complexity [3]. These are therefore ideally suited for generating libraries of small molecules and particularly drug like heterocyclic compounds [4].

In this article, we describe a clean and efficient process for three-component coupling of aldehyde, dimethyl acetylenedicarboxylate and cyclohexyl isocyanide to afford 2-aminofuran derivatives under neutral conditions (Scheme 1).

For example, treatment of *p*-chlorobenzaldehyde with dimethyl acetylenedicarboxylate and cyclohexyl isocyanide in water in the presence of PTC at 80 °C gave dimethyl 2-(4-chlorophenyl)-5-cyclohexylamino-3,4-furandicarboxylate **2a** in 82% yield. The reaction went to completion in a short time (1.5 h). The product thus obtained was isolated by simple extraction with ethyl acetate. Encouraged by the results obtained with *p*-chlorobenzaldehyde, we turned our attention to various aryl, alkyl and heterocyclic aldehydes. Interestingly, various substrates such as aryl, heterocyclic, and aliphatic aldehydes underwent smooth coupling with isocyanide and acetylenedicarboxylate to produce 2-aminofuran derivatives in good yields (entries **a**–**j**, Table 1). The nature of the substituents on the aromatic ring of the substrates shows some effect on this conversion. Aromatic aldehydes such as nitro-, chloro-, fluoro-, and bromo- derivatives gave higher yields than electron-rich counterparts. The reactions also proceeded efficiently with heterocyclic aldehydes such as 2-furaldehyde and thiophene-2-carboxaldehyde (entries **h** and **i**, Table 1). The reaction proceeds probably via the formation of zwitterionic intermediate from DMAD and isocyanide that undergoes addition on the carbon-oxygen double bond and subsequent [1] H shift would result in the formation of 2-aminofuran (Scheme 2).

The anticipated zwitterionic intermediate exhibits enhanced reactivity in water thereby reducing the reaction times and improving the yields significantly. For instance, treatment of thiophene-2-carboxaldehyde with dimethyl acetylenedicar-

* Corresponding author. Tel.: +91 40 27193030; fax: +91 40 27160512.
*E-mail address:* yadav@iict.ap.nic.in (J.S. Yadav).

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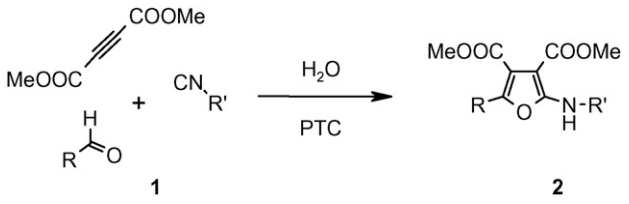
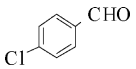
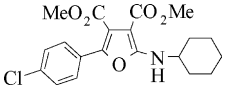
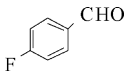
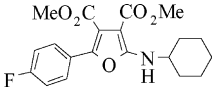
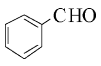
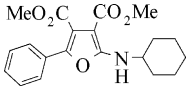
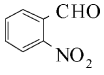
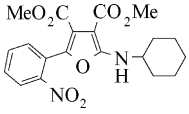
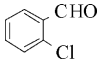
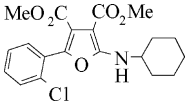
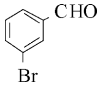
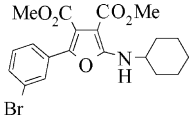
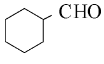
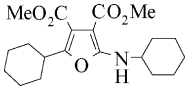
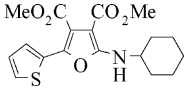
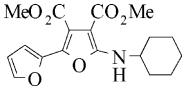
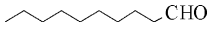
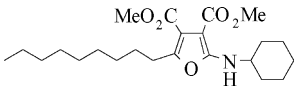



Scheme 1.

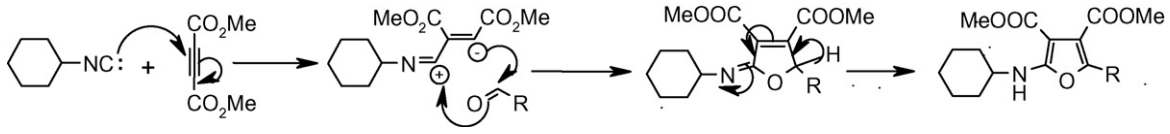
boxyte and cyclohexyl isocyanide in water afforded dimethyl 2-cyclohexylamino-5-(2-furyl)-3,4-furandicarboxylate in 80% yield over 1.5 h whereas the same reaction in refluxing THF gave the desired product in 62% yield after 6 h. The scope and generality of this method is illustrated with respect to various aldehydes and the results are presented in Table 1. The use of water as reaction media helps to avoid the use of high temperature and environmentally unfavorable solvents like benzene thereby making the process economic and environmentally benign.

In summary, we describe water as novel reaction medium for the synthesis of highly functionalized 2-aminofuran derivatives via the coupling of aldehydes with dimethyl acetylenedicarboxylate and cyclohexyl isocyanide. This procedure offers significant advantages such as operational simplicity, mild reaction conditions, enhanced rates, ease of isolation of products, cleaner reaction profiles and eco-friendly nature of the solvent, which makes it useful and attractive strategy for the synthesis of 2-aminofuran derivatives.

Table 1
Preparation of substituted 2-aminofurans using water as solvent

| Entry | Aldehyde | Product[a] | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| **a** |  |  | 1.5 | 82 |
| **b** |  |  | 1.0 | 80 |
| **c** |  |  | 1.5 | 76 |
| **d** |  |  | 1.0 | 81 |
| **e** |  |  | 2.0 | 79 |
| **f** |  |  | 1.5 | 81 |
| **g** |  |  | 1.0 | 83 |
| **h** |  |  | 1.5 | 80 |
| **i** |  |  | 1.0 | 78 |
| **j** |  |  | 1.0 | 82 |

[a] All products were characterized by $^1$H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yields.



Scheme 2.

## 1. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. $^1$H and $^{13}$C NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. TLC was monitored on 0.25 mm pre-coated silica gel plates (60F-254). All the solvents were dried, distilled, and stored under nitrogen prior to use.

### *1.1. General procedure*

A mixture of aldehyde (1 mmol), DMAD (1 mmol) and cyclohexyl isocyanide (1 mmol) in water (5 mL) in the presence of benzyltriethyl ammonium chloride (10 mol%) was stirred at 80 °C for the appropriate time (1–2.0 h). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were concentrated *in vacuo* and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (2:8) to afford the pure 2-aminofuran derivative. The products thus obtained were characterized by comparison of their NMR, IR, Mass, TLC, mixed TLC analysis and physical data with authentic samples. The spectral data of all the products were identical with those of authentic samples [3].

### *1.2. Spectroscopic data*

#### *1.2.1. Dimethyl 2-(4-chlorophenyl)-5-cyclohexylamino-3,4-furandicarboxylate (**2a**)*

Colorless oil, IR (neat) $\upsilon_{max}$: 3360, 2930, 2885, 1735, 1679, 1618, 1473, 1361, 1225, 1098, 829, 761 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.45 (d, 2H, $J$ = 7.8 Hz), 7.32 (d, 2H, $J$ = 7.8 Hz), 6.65 (d, 1H, $J$ = 8.0 Hz, NH), 3.89 (s, 3H), 3.79–3.62 (m, 4H), 2.10–1.3 (m, 10H). FAB mass: *m/z* (%): 392 ($M^+$+1, 22), 361 (9), 208 (8), 147 (11), 109 (12), 95 (29), 81 (41), 69 (59), 55 (100).

#### *1.2.2. Dimethyl 2-cyclohexylamino-5-(4-fluorophenyl)-3,4-furandicarboxylate (**2b**)*

Pale yellow oil, IR (neat) $\upsilon_{max}$: 3405, 2931, 2856,1760, 1732, 1686, 1623, 1597, 1507, 1432, 1272, 1235, 1159, 1114, 1015, 945, 839, 769, 731, 672, 609 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.55–7.45 (m, 2H), 7.10–7.00 (m, 2H), 6.60 (d, 1H, $J$ = 8.0 Hz, NH), 3.85 (s, 3H), 3.75–3.64 (m, 4H), 2.05–1.20 (m, 10H). FAB mass: *m/z* (%): 374 ($M^+$+1, 100), 344 (22), 293 (10), 261 (14), 149 (31), 133 (16), 123 (26), 91 (28), 81 (32), 73 (40), 55 (81).

#### *1.2.3. Dimethyl 2-cyclohexylamino-5-phenyl-3,4-furandicarboxylate (**2c**)*

Pale yellow oil, IR (neat) $\upsilon_{max}$: 3353, 2935, 2854, 1735, 1681, 1613, 1472, 1357, 1222 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.50–7.40 (m, 2H), 7.35–7.15 (m, 3H), 6.65 (d, 1H, $J$ = 8.0 Hz, NH), 3.85 (s, 3H), 3.75–3.65 (m, 4H), 2.10–1.30 (m, 10H). FAB mass: *m/z* (%): 357 ($M^+$, 20), 351 (48), 243 (18), 211 (14), 105 (70), 83 (100), 55 (16), 47 (20).

#### *1.2.4. Dimethyl 2-cyclohexylamino-5-(2-nitrophenyl)-3,4-furandicarboxylate (**2d**)*

Brown viscous liquid, IR (KBr) $\upsilon_{max}$: 3355, 2933, 2857, 1732, 1674, 1618, 1532, 1473, 1358, 1229, 1102, 768 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.80 (d, 1H, $J$ = 7.8 Hz), 7.65–7.40 (m, 3H), 6.65 (d, 1H, $J$ = 8.0 Hz, NH), 3.80–3.70 (m, 6H), 3.55–3.40 (m, 1H), 2.00–1.20 (m, 10H). FAB mass: *m/z* (%): 358 (100), 327 (32), 245 (6), 105 (16), 81 (20), 69 (29), 55 (42).

#### *1.2.5. Dimethyl 2-(2-chlorophenyl)-5-cyclohexylamino-3,4-furandicarboxylate (**2e**)*

Colorless viscous liquid, IR (KBr) $\upsilon_{max}$: 3357, 2932, 2855, 1734, 1676, 1616, 1471, 1363, 1220, 1148, 1102, 946, 892, 771 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.45–7.35 (m, 2H), 7.20–7.30 (m, 2H), 6.67 (d, 1H, $J$ = 8.0 Hz, NH), 3.75 (s, 3H), 3.70–3.55 (m, 4H), 2.00–1.30 (m, 10H). FAB mass: *m/z* (%): 392 ($M^+$ + 1, 22), 357 (9), 294 (25), 208 (8), 142 (11), 109 (12), 95 (29), 81 (41), 69 (59), 55 (100).

#### *1.2.6. Dimethyl 2-(3-bromophenyl)-5-cyclohexylamino-3,4-furandicarboxylate (**2f**)*

Yellow viscous liquid, IR (KBr) $\upsilon_{max}$: 3349, 2934, 2855, 1736, 1681, 1616, 1472, 1359, 1223, 1148, 1103, 880, 772 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.60 (s, 1H), 7.40–7.30 (m, 2H), 7.25–7.15 (m, 1H), 6.65 (d, 1H, $J$ = 8.0 Hz, NH), 3.89 (s, 3H), 3.80–3.60 (m, 4H), 2.10–1.4 (m, 10H). FAB mass: *m/z* (%): 436 ($M^+$, 22), 347 (19), 318 (40), 290 (20), 288 (18), 210 (4), 182 (50), 155 (20), 141 (24), 97 (26), 83 (48), 55 (100).

#### *1.2.7. Dimethyl 2-cyclohexyl-5-cyclohexylamino-3,4-furandicarboxylate (**2g**)*

Pale yellow liquid, IR (KBr) $\upsilon_{max}$: 3346, 2931, 2857, 1728, 1668, 1621, 1470, 1365, 1222, 1100, 1080, 775 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 3.85–3.65 (m, 8H), 1.85–1.55 (m, 8H), 1.45–1.10 (m, 12H). FAB mass: *m/z* (%): 400 ($M^+$, 19), 303 (30), 97 (10), 85 (70), 83 (100), 69 (30), 55 (50), 43 (60).

#### *1.2.8. Dimethyl 2-cyclohexylamino-5-(2-thienyl)-3,4-furandicarboxylate (**2h**)*

Light yellow oil, IR (KBr) $\upsilon_{max}$: 3356, 2934, 2855, 1731, 1676, 1616, 1472, 1364, 1232, 1148, 1101, 772 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.30–7.35 (m, 1H), 7.26–7.21 (m, 1H),

6.98–7.02 (m, 1H,), 6.67 (d, 1H, $J = 8.0$ Hz, NH), 3.90 (s, 3H), 3.79 (s, 1H), 3.70–3.60 (m, 1H), 2.10–1.25 (m, 10H). FAB mass: *m/z* (%): 364 ($M^+$+1, 100), 333 (26), 249 (6), 111 (9), 95 (14), 83 (20), 55 (37).

### *1.3. Dimethyl 2-cyclohexylamino-5-(2-furyl)-3,4-furandicarboxylate (**2i**)*

Brown oil, IR (KBr) $\upsilon_{max}$: 3349, 3130, 2930, 2856, 1732, 1676, 1607, 1483, 1365, 1269, 1237, 1220 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.40 (d, 1H, $J = 1.9$ Hz), 6.66 (d, 1H, $J = 8.0$ Hz, NH), 6.60 (d, 1H, $J = 5.0$ Hz), 6.40 (dd, 1H, $J = 5.0$, 1.9 Hz), 3.89 (s, 3H), 3.75–3.65 (m, 4H), 2.10–1.4 (m, 10H). FAB mass: *m/z* (%): 367 ($M^+$, 100), 349 (21), 265 (10), 111 (9), 95 (14), 83 (20), 55 (37).

### *1.4. Dimethyl 2-cyclohexylamino-5-nonyl-3,4-furandicarboxylate (**2j**)*

Colorless liquid, IR (KBr) $\upsilon_{max}$: 3349, 2927, 2854, 1731, 1673, 1622, 1468, 1364, 1219, 1105, 1074, 773 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 6.60 (d, 1H, $J = 8.0$ Hz, NH), 3.80 (s, 3H), 3.70 (s, 3H), 3.60–3.40 (m, 1H), 2.60 (t, 2H, $J = 1.9$ Hz), 2.00–0.80 (m, 27H). FAB mass: *m/z* (%): 407 ($M^+$, 23), 97 (10), 85 (70), 83 (100), 69 (30), 55 (50), 43 (60).

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