A convenient and clean procedure for the synthesis of pyran derivatives in aqueous media catalysed by TEBAC

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A clean and simple synthesis of 6-amino-5-cyano-4-aryl-2-methyl-4*H*-pyran-3-carboxylate derivatives was accomplished in high yields via the reaction of arylmethylidenemalononitriles with acetoacetate in aqueous media catalysed by triethylbenzylammonium chloride (TEBAC). The structures were established by spectroscopic data and further confirmed by X-ray analysis.

Keywords: pyran, arylmethylidenemalononitrile, acetoacetate, aqueous media, TEBAC

Many pyran derivatives exhibit a wide spectrum of pharmacological activities and biological activities at melanocortin receptors and are being used in the design of peptidomimetics relating to a tripeptide structure,[1] such as fungicidal, insecticidal and acaricidal activity,[2] antiviral activity,[3] miticidal activity,[4] stimulant activity,[5] and anticonvulsant activity.[6] Because of the toxic and volatile nature of many organic solvents, ionic liquids and aqueous media are emerging as effective solvents for 'green' processes. However, the high cost of most conventional room temperature ionic liquids and apprehension about their toxicity led us to explore these potential active compounds under environmentally friendly conditions. Particularly, we focused our attention on the use of water as reaction medium. They were considered promising and attractive substitutes for volatile organic solvents and were widely used in the green chemistry area, since Breslow,[7] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in the 1980s. There has been growing recognition that water is an attractive medium for many organic reactions resulting less expensive, less dangerous and environmentally friendly, such as Diels–Alder reactions,[8] Claisen Rearrangement reactions,[9] Reformatsky reactions[10] and Pinacol-coupling reactions.[11] As part of our current studies on the development of new routes to heterocyclic systems[12], we now report an efficient and clean synthetic route to 6-amino-5-cyano-4-aryl-2-methyl-4*H*-pyran-3-carboxylate derivatives in aqueous media catalysed by TEBAC by the reaction of arylmethylidenemalononitriles and acetoacetate.

When the reaction of arylmethylidenemalononitriles **1** with acetoacetate **2** were performed in water in the presence of TEBAC at 100 °C, high yields of 6-amino-5-cyano-4-aryl-2-methyl-4*H*-pyran-3-carboxylate derivatives **3** were obtained (Scheme 1). The results are summarised in Table 1.

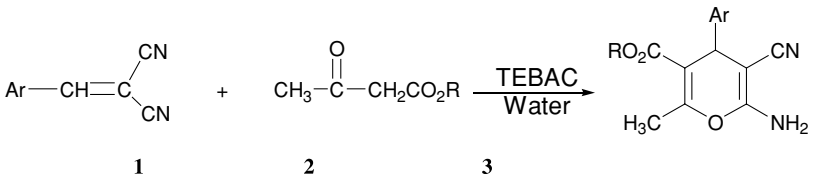
In order to apply this reaction to a library synthesis, various kinds of arylmethyl- idenemalononitriles **1** and acetoacetate **2** were subjected to give the corresponding 6-amino-5-cyano-4-aryl-2-methyl-4*H*-pyran-3-carboxylate derivatives **3**, and representative examples are shown in Table 1. All of the arylmethylidenemalononitriles **1** containing electronic-withdrawing groups (such as nitro group, halide) or electronic-donating groups (such as alkoxyl group) were employed and reacted well to give the corresponding products **3** in excellent yields under the same reactions condition, so we concluded that no obvious effect of electron and nature of substituents on the aromatic ring were observed.

Table 1 The results on the reaction of **1** and **2** in water at 100 °C[a]

Entry	Ar	R	Products	Time/h	Yields/%[b]
1	C_6H_5	Et	**3a**	12	97
2	3-ClC_6H_4	Et	**3b**	10	97
3	2-$NO_2C_6H_4$	Et	**3c**	8	96
4	4-BrC_6H_4	Et	**3d**	8	95
5	2-ClC_6H_4	Et	**3e**	8	93
6	3-$NO_2C_6H_4$	Me	**3f**	8	94
7	3,4-$Cl_2C_6H_3$	Et	**3g**	6	99
8	4-$CH_3OC_6H_4$	Me	**3h**	12	95
9	2,4-$Cl_2C_6H_3$	Me	**3i**	6	96
10	3,4-$Cl_2C_6H_3$	Me	**3j**	6	99

[a]Reaction condition: 10 ml water and 0.2 g TEBAC, 2 mmol **1** and 2 mmol **2**.
[b]Isolated yields.

The isolated 6-amino-5-cyano-4-aryl-2-methyl-4*H*-pyran-3-carboxylate derivatives **3** were completely characterised by IR, ^{1}H NMR and elemental analyses. The analyses were in agreement with their structures. The IR spectra for **3a** exhibited sharp bands at 3404, 3329 cm^{-1} (NH_2), 2190 (CN), 1693 cm^{-1} (C=O). The ^{1}H NMR spectrum of **3a** exhibited a singlet identified methine (4.44) and along with multiplets (7.19–7.32) for aromatic protons. The NH_2 proton resonance at 4.46 disappeared after addition of D_2O to the $CDCl_3$ solution of **3a**. In order to further confirm the structure of the product, the X-ray analysis[13] of **3a** was carried out. The structure of **3a** is shown in Fig. 1.



1 **2** **3**

Scheme 1

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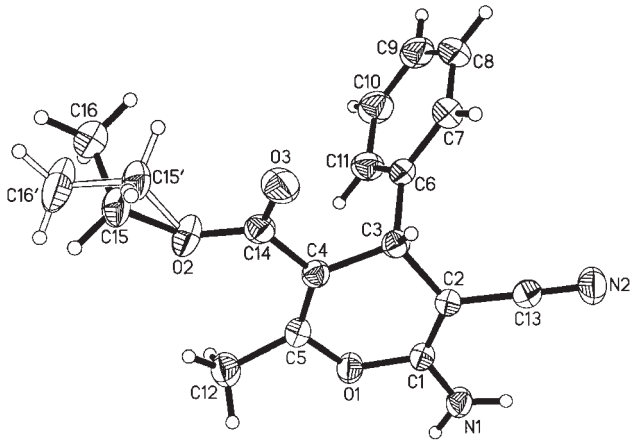

Fig. 1 The crystal structure of the product **3a**.

Finally the reuse of the water and TEBAC was studied. At completion monitored by TLC, the reaction mixture was allowed to cool to room temperature, the solid of the products was isolated by filtration, and the filtrate of the water together with TEBAC could be reused directly. Investigations by using **1a** and **2** as model substrates showed that successive reuse of the recovery water and TEBAC. A summary of the reuse of water and TEBAC is shown in Table 2. Even in the fourth round the yield of the product **3** is fairly high.

In conclusion, an efficient green chemistry method for the synthesis of 6-amino-5-cyano-4-aryl-2-methyl-4*H*-pyran-3-carboxylate derivatives by condensation of arylmethylidenemalononitriles and acetoacetate was successfully established, this new method has the advantages of good yields, mild reaction conditions, easy work-up, inexpensive reagents and an environmentally friendly procedure.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a TENSOR 27 spectrometer in KBr. ^{1}H NMR spectra were obtained for solution in DMSO-d_6 or $CDCl_3$ with Me_4Si as internal standard using a Bruker-400 spectrometer. Elemental analyses were carried out using Carlo Erba 1110 analyser. X-ray diffraction was measured on a Siemens P4 diffractometer.

General procedure

A suspension of a mixture of arylmethylidenemalononitriles **1** (2 mmol), acetoacetate **2** (3 mmol) and TEBAC (0.1 g) was stirred in water (10 ml) at 100 °C for 6–12 h. The crystalline power formed was collected by filtration, washed with water and recrystallised from DMF and water to give pure 6-amino-5-cyano-4-aryl-2-methyl- 4*H*-pyran-3-carboxylate derivatives **3**.

Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (**3a**): M. p. 194–196 °C (Lit.[14] 197 °C). IR: ν_{max} (KBr, cm^{-1}) 3404, 3329, 2967, 2190, 1693, 1610, 1541, 1457, 1414, 736, 698. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.09 (t, *J* = 7.2 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.03 (q, *J* = 7.2 Hz, 2H, CH_2), 4.44 (s, 1H, CH), 4.46 (s, 2H, NH_2), 7.19–7.23 (m, 3H, ArH), 7.27–7.32 (m, 2H, ArH).

Ethyl 6-amino-4-(3-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (**3b**): M. p. 177–178 °C. IR: ν_{max} (KBr, cm^{-1}) 3401, 3327, 2193, 1696, 1649, 1603, 1591, 1473, 779, 709. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.15 (t, *J* = 7.2 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.10 (q, *J* = 7.2 Hz, 2H, CH_2), 4.45 (s, 1H, CH), 4.56 (s, 2H, NH_2), 7.13–7.53 (m, 4H, ArH); Anal. calcd for $C_{16}H_{15}ClN_2O_3$: C 60.29, H 4.74, N 8.79; found C 60.08, H 4.77, N 8.90.

Ethyl 6-amino-5-cyano-2-methyl-4-(2-nitrophenyl)-4H-pyran-3-carboxylate (**3c**): M. p. 181–183 °C; IR: ν_{max} (KBr, cm^{-1}) 3455, 3296, 2209, 1718, 1602, 1530, 728. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 0.99 (t, *J* = 7.2 Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.99 (q, *J* = 7.2 Hz, 2H, CH_2), 4.64 (s, 2H, NH_2), 5.28 (s, 1H, CH), 7.36–7.39 (m, 2H, ArH), 7.58 (t, *J* = 7.2 Hz, 1H, ArH), 7.83 (d, *J* = 8.4 Hz, 1H, ArH); Anal. calcd for $C_{16}H_{15}N_3O_5$: C 58.36, H 4.59, N 12.76; found C 58.21, H 4.66, N 12.90.

Table 2 Study on the reuse of water and TEBAC[a]

Entry	Temperature/°C	Reaction time/h	Yields/%[b]
1	100	12	97
2	100	12	97
3	100	12	96
4	100	12	92

[a]Reaction condition: 10 ml water and TEBAC, 2 mmol **1a** and 2 mmol **2**.
[b]Isolated yields.

Ethyl 6-amino-4-(4-bromophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (**3d**): M. p. 177–179 °C; IR: ν_{max} (KBr, cm^{-1}) 3410, 3330, 2981, 2195, 1692, 1609, 1541, 1487, 836.^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.15 (t, *J* = 6.8 Hz, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.07 (q, *J* = 6.8 Hz, 2H, CH_2), 4.44 (s, 1H, CH), 4.53 (s, 2H, NH_2), 7.11 (d, *J* = 8.4 Hz, 2H, ArH), 7.45 (d, *J* = 8.4 Hz, 2H, ArH); Anal. calcd for $C_{16}H_{15}BrN_2O_3$: C 52.91, H 4.16, N 7.71; found C 52.78, H 4.22, N 7.80.

Ethyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (**3e**): M. p. 190–192 °C (Lit.[15] 185 °C); IR: ν_{max} (KBr, cm^{-1}) 3429, 3333, 2981, 2195, 1687, 1541, 1473, 744. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.08 (t, *J* = 7.2 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.02 (q, *J* = 7.2 Hz, 2H, CH_2), 4.51 (s, 2H, NH_2), 5.08 (s, 1H, CH), 7.15–7.51 (m, 4H, ArH).

Methyl 6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4H-pyran-3-carboxylate (**3f**): M. p. 204–206 °C; IR: ν_{max} (KBr, cm^{-1}) 3402, 3331, 2972, 2193, 1699, 1676, 1608, 1531, 1417, 742, 718. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 2.44 (s, 3H, CH_3), 3.63 (s, 3H, CH_3O), 4.60 (s, 1H, CH), 4.62 (s, 2H, NH_2), 7.52 (t, *J* = 8.0 Hz, 1H, ArH), 7.61 (d, *J* = 8.0 Hz, 1H, ArH), 8.07 (d, *J* = 1.2 Hz, 1H, ArH), 8.13(dd, *J* = 8.0 Hz, *J'* = 1.2 Hz, 1H, ArH); Anal. calcd for $C_{15}H_{13}N_3O_5$: C 57.14, H 4.16, N 13.33; found C 57.01, H 4.22, N 13.45.

Ethyl 6-amino-5-cyano-4-(3,4-dichlorophenyl)-2-methyl-4H-pyran-3-carboxylate (**3g**): M. p. 180–182 °C (Lit.[16] 184–186 °C); IR: ν_{max} (KBr, cm^{-1}) 3411, 3328, 2978, 2197, 1683, 1610, 1541, 1472, 765, 730. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.18 (t, *J* = 6.8 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.04 (q, *J* = 6.8 Hz, 2H, CH_2), 4.44 (s, 1H, CH), 4.58 (s, 2H, NH_2), 7.09 (dd, *J* = 8.4 Hz, *J'* = 2.0 Hz, 1H, ArH), 7.40 (d, *J* = 8.4 Hz, 1H, ArH), 7.46 (d, *J* = 8.4 Hz, 1H, ArH).

Methyl 6-amino-5-cyano-4-(4-methoxyphenyl)-2-methyl-4H-pyran-3-carboxylate (**3h**): M. p. 221–222 °C; IR: ν_{max} (KBr, cm^{-1}) 3408, 3334, 3226, 2223, 1714, 1662, 1617, 1589, 1517, 1457, 1408, 842. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 2.34 (s, 3H, CH_3), 3.59 (s, 3H, CH_3O), 3.80 (s, 3H, CH_3O), 4.00 (s, 2H, NH_2), 5.73 (s, 1H, CH), 7.04 (d, *J* = 8.8 Hz, 2H, ArH), 7.45 (d, *J* = 8.8 Hz, 2H, ArH); Anal. calcd for $C_{16}H_{16}N_2O_4$: C 63.99, H 5.37, N 9.33; found C 64.12, H 5.40, N 9.38.

Methyl 6-amino-5-cyano-4-(2,4-dichlorophenyl)-2-methyl-4H-pyran-3-carboxylate (**3i**): M. p. 178–180 °C; IR: ν_{max} (KBr, cm^{-1}) 3450, 3325, 2947, 2209, 1716, 1682, 1604, 1561, 1507, 1473, 1403, 846, 768. ^{1}H NMR δ_H (DMSO-d_6, 400 MHz): 2.33 (s, 3H, CH_3), 3.49 (s, 3H, CH_3O), 4.85 (s, 1H, CH), 7.02 (s, 2H, NH_2), 7.23 (q, *J* = 8.4 Hz, 1H, ArH), 7.37–7.41 (m, 1H, ArH), 7.54–7.56 (m, 1H, ArH); Anal. calcd for $C_{15}H_{12}Cl_2N_2O_3$: C 53.12, H 3.57, N 8.26; found C 53.04, H 3.70, N 8.38.

Methyl 6-amino-5-cyano-4-(3,4-dichlorophenyl)-2-methyl-4H-pyran-3-carboxylate (**3j**): M. p. 174–175 °C; IR: ν_{max} (KBr, cm^{-1}) 3410, 3329, 2192, 1676, 1607, 1559, 1472, 764. ^{1}H NMR δ_H (DMSO-d_6, 400 MHz) 2.32 (s, 3H, CH_3), 3.54 (s, 3H, CH_3O), 4.35 (s, 1H, CH), 7.05 (s, 2H, NH_2), 7.14–7.17 (m, 1H, ArH), 7.36–7.38 (m, 1H, ArH), 7.59 (q, *J* = 8.4 Hz, 1H, ArH); Anal. calcd for $C_{15}H_{12}Cl_2N_2O_3$: C 53.12, H 3.57, N 8.26; found C 53.20, H 3.52, N 8.30.

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13 Crystallographic data for the structure of **3a** reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication with No. CCDC-270287, Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). X-ray crystallography for **3a**: Empirical formula $C_{16}H_{16}N_2O_3$, F_W = 284.31, T = 289(2) K, triclinic, space group P-1, a = 8.1402(16) Å, b = 9.3393(19) Å, c = 11.206(2) Å, α = 107.047(3) °, β = 103.066(4) °, γ = 106.257(3) °, V = 736.5(3) Å^3, Z = 2, D_c = 1.282 Mg/m^3, λ*(MoKα)* = 0.71073 Å, μ = 0.090 mm^{-1}, F(000) = 300. 2.46 ° < θ < 25.00 °, S = 0.968, Largest diff. Peak and hole: 0.152 and –0.154 e. Å^{-3} The structure was solved by direct method using SHELXTL[17] program and expanded using Fourier technique. The non-hydrogen atoms were refined anisotropically, the hydrogen atoms were positioned geometrically and refined as riding except for H1A and H1B. A full-matrix least-squares refinement gave final R = 0.0436 and ωR = 0.1020 with $\omega = 1/[\sigma^2 (F_o^2) + (0.056P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$.
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