Organocatalytic clean synthesis of densely functionalized 4H-pyrans by bifunctional tetraethylammonium 2-(carbamoyl)benzoate using ball milling technique under mild conditions

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ABSTRACT
A green and simple method has been developed for efficient preparation of diverse annulated 2-amino-3-cyano-4H-pyran derivatives in the presence of a low loading of tetraethylammonium 2-(carbamoyl)benzoate (TEACB), as a bifunctional organocatalyst, under solvent-free conditions using the ball milling technique. This procedure is a clean, transition-metal-free, and environmentally friendly approach that offers many advantages including short reaction times, high to quantitative yields, low cost, and straightforward work-up.

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Introduction
Designing and conducting chemical reactions through “green” experimental protocols is an enormous challenge that chemists have to confront to improve the quality of the environment for present and future generations. An ultimate goal in green chemistry is to eliminate or minimize the use of volatile organic solvents in modern organic synthesis. Hence, development of new synthetic methodologies under solvent-free conditions is an important area of research with growing popularity. The interest for solvent-free reactions arises from advantages such as reducing or eliminating solvent usage and consequently low pollution and costs, simplicity in relevant processes, and handling (1–4). These factors are especially important in industry. On the other hand, multicomponent reactions (MCRs), defined as any process in which three or more reactants combine in one pot to

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generate a product containing all or most atoms of the starting materials, are highly atom efficient (5–8). Thus, an ideal MCR involves the simultaneous addition of reactants, catalyst, or reagents at the beginning of the reaction and requires that all reactants couple in an exclusive ordered mode under the same reaction conditions (5–8). Their superior atom economy, resulting in substantial minimization of waste, labour, time, and cost as well as high efficiency, mild conditions, high convergence, and their general compatibility with green solvents, would justify a central place in the toolbox of green synthetic methodologies (5–8). Therefore, academic and industrial research groups have increasingly focused on the use of MCRs for synthesizing a broad range of products especially important heterocyclic compounds such as 4H-pyran derivatives nowadays (9–12). Recently, several techniques for efficient application of solvent-free conditions or MCRs have been developed.

**Figure 1.** Structures of some 2-amino-4H-pyrans with diverse biological activities.

**Scheme 1.** Three-component reaction of different phenols or enols with aromatic aldehydes and malononitrile catalyzed by TEACB (5) under ball milling conditions at ambient temperature.

**Table 1.** Optimization of the reaction conditions for the preparation of 2-amino-4-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-4H-benzogchromene-3-carbonitrile (9a).a

| Entry | Catalyst (mol%) | Conditions | Time (min) | Yieldb (%) |
|-------|----------------|------------|------------|------------|
| 1     | LIPINOd (10)   | Ball milling, ambient temperature | 40         | Tracec     |
| 2     | LIPINOd (10)   | Ball milling, ambient temperature | 30         | 20         |
| 3     | NAPINOe (10)   | Ball milling, ambient temperature | 30         | 45         |
| 4     | POPINOf (10)   | Ball milling, ambient temperature | 10         | 75         |
| 5     | TEACB (1)      | Ball milling, ambient temperature | 5          | 80         |
| 6     | TEACB (2)      | Ball milling, ambient temperature | 5          | 98g        |

aReaction conditions: 2-hydroxynaphthalene-1,4-dione (6, 1 mmol), 4-chlorobenzaldehyde (7a, 1 mmol), and malononitrile (8, 1.0 mmol).

bThe yields refer to the isolated product 9a.

cThe Knoevenagel condensation product V was formed in almost quantitative yield.

dLithium phthalimide-N-oxyl.

eSodium phthalimide-N-oxyl.

fPotassium phthalimide-N-oxyl.

gQuantitative conversion of the substrates to the desired product 9a was observed. Simple trituration of the reaction mixture in water and its subsequent filtering afforded essentially pure solid 9a.
individually. However, when these two wings of green chemistry can be combined, an excellent green chemistry protocol is expected (13–16).

One of the most important processes to combine solvent-free reactions and MCRs is the use of ball milling solid-state mechanochemical techniques (17–19). The ball milling technique has also received increasing attention in organic synthesis in recent years. Subsequently, some specific books and review papers have been published on the topic. Some typical examples include the carbon–carbon or carbon–heteroatom bond formation, oxidation by solid oxidants, asymmetric organocatalytic reactions, dehydrogenative coupling, and peptide or polymeric material synthesis (9, 10–12). Furthermore, organocatalysis, namely the use of small organic molecules to catalyze organic transformations, is a relatively new and popular field within the domain of organic synthesis. Once the field of organocatalysis had been publicly defined, it grew quickly (32–37). Although the impact of transition-metal-based catalysts on chemical synthesis cannot be completely understated, some metal-based systems can be expensive, toxic, and sensitive to air or moisture (38–40). Hence, the advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste (41–45).

On the other hand, the 4H-pyran derivatives show various pharmacological properties such as spasmylytic, diuretic, anticoagulant, anticancer, and antianaphylactic activities (9, 10–12). Such diverse biological features have made 4H-pyran derivatives important for further exploration in modern medicinal and combinatorial chemistry (46, 47). For instance, 2-amino-4H-chromene derivatives, such as compounds 1 and 2, have been known as anticancer therapeutic agents. On the other

Table 2. Three-component synthesis of different 2-amino-5,10-dihydro-5,10-dioxo-4H-benzo[g]chromene-3-carbonitrile derivatives (9a–j) via condensation of 2-hydroxynaphthalene-1,4-dione (6), various aldehydes 7a–j and malononitrile (8) in the presence of TEACB (5) using ball milling technique at ambient temperature.²

| Entry | Aldehyde 7 | Time (min) | Product 9 | Isolated yield (%)² M.P. (Obd.) (°C) | M.P. (Lit.) (°C) | Reference |
|-------|------------|------------|----------|----------------|----------------|-----------|
| 1     | 4-Chlorobenzaldehyde (7a) | 5          | 9a       | 98             | 243–244       | 241–243   | (10–12) |
| 2     | 2-Chlorobenzaldehyde (7b) | 5          | 9b       | 98             | 248–250       | 250–251   | (10–12) |
| 3     | 4-Fluorobenzaldehyde (7c) | 5          | 9c       | 98             | 244–246       | 243–245   | (10–12) |
| 4     | 4-Bromobenzaldehyde (7d) | 5          | 9d       | 98             | 249–251       | 248–250   | (10–12) |
| 5     | 4-Nitrobenzaldehyde (7e) | 4          | 9e       | 98             | 232–236       | 234–235   | (10–12) |
| 6     | Benzaldehyde (7f)          | 6          | 9f       | 97             | 263–264       | 264–266   | (10–12) |
| 7     | 4-Methylbenzaldehyde (7g) | 6          | 9g       | 97             | 240–242       | 241–243   | (10–12) |
| 8     | 4-Hydroxybenzaldehyde (7h) | 7          | 9h       | 97             | 258–260       | 256–259   | (10–12) |
| 9     | 4-Methoxybenzaldehyde (7i) | 7          | 9i       | 96             | 243–245       | 244–246   | (10–12) |
| 10    | 4-Hydroxy-3-methoxy benzaldehyde (7j) | 9          | 9j       | 96             | 245–247       | 245–248   | (10–12) |

²Reaction conditions: 2-hydroxynaphthalene-1,4-dione (6, 1 mmol), aldehydes (7a–j, 1 mmol), malononitrile (8, 1.0 mmol), and TEACB (5, 2 mol%).

²All compounds are known and their structures were established from their spectral data and melting points as compared with authentic samples or literature values.

²Simple trituration of the reaction mixture in water and its subsequent filtering afforded essentially pure solid 9a–j.
hand, compound 3 serves as a precursor for the blood anticoagulant warfarin while compound 4 shows an antibacterial activity (Figure 1) (46, 47).

Due to the important aforementioned properties of pyran derivatives, considerable attention has been focused on the development of environmentally friendly methodologies for the synthesis of 2-amino-4H-pyran scaffold by cyclization of an aromatic aldehyde, malononitrile and diverse phenolic or enolizable C–H-activated acidic compounds. Indeed, malononitrile has been used as a nucleophile in organic synthesis (48). A literature survey shows that several modified methods have been reported using different catalysts such as tungstic acid functionalized mesoporous SBA-15 (49), TiCl4 (50), KSF (51), heteropolyacid (52), carbon nanotube-supported Fe3O4 nanoparticles or CoFe2O4 and ZnFe2O4 nano-powders (53–55), basic-functionalized ionic liquids (56), piperidine under microwave irradiation (57), amine-thiourea (58), 4-dimethylaminopyridine, functionalized polyacrylonitrile fiber (59, 60), per-6-amino-β-cyclodextrin (61), tetrabutylammonium bromide (62, 63), hydrotalcite (64), nanozeolite clinoptilolite (65), K2CO3 (66, 67), and chitosan (68). However, some of these protocols require highly corrosive, fuming or expensive catalysts, odorous amines, high temperatures using volatile or toxic solvents, long reaction times, multi-step preparation of the catalysts, troublesome waste discarding, and affordable products with only

![Scheme 3](image_url)

**Scheme 3.** One-pot three-component reaction of 4-hydroxycoumarin (10), aldehydes 7a–j, and malononitrile (8) catalyzed by TEACB (5) using the ball milling technique at ambient temperature.

**Table 3.** Three-component synthesis of different 2-amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives (11a–j) via condensation of 4-hydroxycoumarin (10), various aldehydes 7a–k and malononitrile (8) in the presence of TEACB (5) using the ball milling technique at ambient temperature.a

| Entry | Aldehyde 7 | Time (min) | Product 11 | Isolated yield (%) | M.P. (Obsd.) (°C) | M.P. (Lit.) (°C) | Reference |
|-------|------------|------------|------------|-------------------|-------------------|------------------|------------|
| 1     | 4-Chlorobenzaldehyde (7a) | 5          | 11a         | 97                | 264–266           | 266–267         | (10–12)   |
| 2     | 2-Chlorobenzaldehyde (7b)  | 5          | 11b         | 96                | 261–263           | 263–264         | (72)       |
| 3     | 4-Bromobenzaldehyde (7d)  | 5          | 11c         | 97                | 251–253           | 252–254         | (57)       |
| 4     | 4-Nitrobenzaldehyde (7e)  | 4          | 11d         | 97                | 249–251           | 250–252         | (10–12)   |
| 5     | 3-Nitrobenzaldehyde (7k)  | 5          | 11e         | 98                | 262–265           | 263–265         | (10–12)   |
| 6     | Benzaldehyde (7f)         | 5          | 11f         | 96                | 263–264           | 261–263         | (10–12)   |
| 7     | 4-Methylbenzaldehyde (7g) | 6          | 11g         | 95                | 256–258           | 257–259         | (10–12)   |
| 8     | 4-Hydroxybenzaldehyde (7h) | 6       | 11h         | 95                | 256–258           | 257–260         | (10–12)   |
| 9     | 4-Methoxybenzaldehyde (7i) | 7         | 11i         | 96                | 233–236           | 235–237         | (10–12)   |
| 10    | 4-Hydroxy-3-methoxybenzaldehyde (7j) | 9     | 11j         | 94                | 257–259           | 275–277         | (10–12)   |

*aReaction conditions: 4-hydroxycoumarin (10, 1 mmol), aldehydes (7a–k 1 mmol), malononitrile (8, 1.0 mmol), and TEACB (5, 2 mol%).

*bAll compounds are known and their structures were established from their spectral data and melting points as compared with authentic samples or literature values.

*cSimple trituration of the reaction mixture in water and its subsequent filtering afforded essentially pure solid 11a–j.
modest yields. Therefore, the introduction of milder, faster, and more ecofriendly methods, accompanied with higher yields, is needed for the synthesis of 2-amino-4H-pyran.

In continuation of our interest to develop the catalytic scope of TEACB (5), as an effective, bifunctional organocatalyst, easy to handle and readily available catalyst, for the synthesis of cyanohydrin trimethylsilyl ethers (69), cyclotrimerization of isocyanates (70), and fabrication of cross-linked poly(urethane-isocyanurate) networks (71), we decided to investigate a transition-metal-free method for the synthesis of 2-amino-4H-pyran scaffold with diverse substituents using a ball mill under a solvent-free condition (Scheme 1).

Results and discussion

To find the optimized conditions, a systematic study using different organocatalysts was carried out for the reaction of 2-hydroxynaphthalene-1,4-dione (6), 4-chlorobenzaldehyde (7a), and malononitrile (8) (1:1:1 mole ratio) as the model reaction. The results are summarized in Table 1. In the absence of any catalyst, only a poor yield of the desired 2-amino-4-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (9a) was obtained under ball milling conditions at ambient temperature (Entry, 1, Table 1). However, the use of phthalimide-N-oxyl (PINO) anion with different counter cations at 10 mol% loading slightly improved the yield of desired product 9a under ball milling conditions at ambient temperature (Scheme 1).

Table 4. Three-component synthesis of different 2-amino-7-hydroxy-4H-chromene-3-carbonitrile derivatives (13a-j) via condensation of resorcinol (12), aldehydes 7a–m, malononitrile (8) in the presence of TEACB (5) using the ball milling technique at ambient temperature.\(^a\)

| Entry | Aldehyde 7 | Time (min) | Product 13 | Isolated yield (%) | M.P. (Obsd.) (°C) | M.P. (Lit.) (°C) | Reference |
|-------|------------|------------|------------|-------------------|-------------------|-----------------|-----------|
| 1     | 4-Chlorobenzaldehyde (7a) | 5          | 13a        | 98                | 160–161           | 162–163         | (10–12)   |
| 2     | 2-Chlorobenzaldehyde (7b) | 5          | 13b        | 96                | 187–188           | 189–190         | (10–12)   |
| 3     | 4-Fluorobenzaldehyde (7c) | 5          | 13c        | 97                | 192–194           | 190–192         | (10–12)   |
| 4     | 4-Bromobenzaldehyde (7d) | 5          | 13d        | 97                | 225–227           | 227–229         | (10–12)   |
| 5     | 4-Nitrobenzaldehyde (7e) | 4          | 13e        | 98                | 230–232           | 232–234         | (73)      |
| 6     | 3-Nitrobenzaldehyde (7k) | 4          | 13f        | 98                | 170–171           | 169–170         | (73)      |
| 7     | Benzaldehyde (7f)       | 6          | 13g        | 96                | 229–231           | 230–232         | (10–12)   |
| 8     | Furfural (7l)           | 7          | 13h        | 95                | 183–185           | 182–184         | (10–12)   |
| 9     | Thiophen-2-carbaldehyde (7m) | 10  | 13i        | 95                | 186–188           | 185–187         | (10–12)   |

\(^a\)Reaction conditions: resorcinol (12, 1 mmol), aldehydes (7a–m 1 mmol), malononitrile (8, 1.0 mmol) and TEACB (5, 2 mol%).

\(^b\)All compounds are known and their structures were established from their spectral data and melting points as compared with authentic samples or literature values.

\(^c\)Simple trituration of the reaction mixture in water and its subsequent filtering afforded essentially pure solid of 13a-j.
conditions. POPINO afforded higher yield compared to other salts including Li\(^+\) and Na\(^+\) (Entries 2–4, Table 1). Then, the effect of TEACB (5), as a bifunctional organocatalyst, on the completion of the reaction was studied in the next step (Entries 5 and 6, Table 1).

The obtained results demonstrated that higher yields in shorter reaction times can be obtained in the presence of 2 mol% catalyst loading of TEACB (5) using the ball milling technique at ambient temperature (Entry 6, Table 1). Therefore, TEACB (5) loading of 2 mol% under solvent-free ball milling conditions was developed to other derivatives of aromatic aldehydes (7a–j) for the synthesis of the desired 2-amino-4\(H\)-chromene derivatives 9a–j (Scheme 2).

In order to generalize the optimum conditions, different derivatives of 2-amino-5,10-dihydro-5,10-dioxo-4\(H\)-benzo[g]chromene-3-carbonitrile (9a–j) were prepared from the one-pot reaction mixture of 2-hydroxynaphthalene-1,4-dione (6), aldehydes 7a–j, and malononitrile (8) catalyzed by TEACB (5) using the ball milling technique at ambient temperature. The results are summarized in Table 2. As it is shown in Table 2, aromatic aldehydes with electron withdrawing groups (Entries 1–5) accelerate the reaction compared to the electron-donating groups (Entries 7–10, Table 2).

In the next step, various derivatives of 2-amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (11a–j) were synthesized from the one-pot reaction mixture of 4-hydroxycoumarin (10), aromatic aldehydes 7a–k, and malononitrile (8) in the presence of catalytic amount of TEACB (5, 2 mol%) using the ball milling technique (Scheme 3). The results are summarized in Table 3. The trend of reactivity for different aldehydes is similar to the previous ones in the case of 2-hydroxynaphthalene-1,4-dione (6).

After that, resorcinol (12) was used as an enolic component for the synthesis of different 2-amino-7-hydroxy-4\(H\)-chromene-3-carbonitrile derivatives (13a–j).

### Table 5. Three-component synthesis of different fused aromatic ring of 2-amino-4\(H\)-chromene-3-carbonitrile derivatives 15a–h via condensation of 2-naphthol (14), aldehydes 7a–n, malononitrile (8) in the presence of TEACB (5) using ball milling technique at ambient temperature.\(^a\)

| Entry | Aldehyde 7 | Time (min) | Product 15a–h | Isolated yield (%)\(^c\) | M.P. (Obsd.) (°C) | M.P. (Lit.) (°C) | Reference |
|-------|------------|------------|----------------|--------------------------|------------------|-----------------|-----------|
| 1     | 4-Chlorobenzaldehyde (7a) | 5          | 15a           | 97                       | 207–208          | 206–208         | (10–12)   |
| 2     | 2-Chlorobenzaldehyde (7b) | 5          | 15b           | 96                       | 256–258          | 259–261         | (10–12)   |
| 3     | 4-Bromobenzaldehyde (7d) | 5          | 15c           | 97                       | 238–240          | 241–243         | (10–12)   |
| 4     | 4-Nitrobenzaldehyde (7e) | 4          | 15d           | 97                       | 187–189          | 188             | (74)      |
| 5     | 3-Nitrobenzaldehyde (7k) | 4          | 15e           | 98                       | 232–234          | 232–235         | (75)      |
| 6     | 4-Cyanobenzaldehyde (7n) | 5          | 15f           | 98                       | 257–259          | 258–260         | (10–12)   |
| 7     | Benzaldehyde (7f)        | 7          | 15g           | 96                       | 283–285          | 280–282         | (10–12)   |
| 8     | 4-Methoxybenzaldehyde (7i) | 7          | 15h           | 95                       | 184–185          | 182–183         | (10–12)   |

\(^a\)Reaction conditions: 2-naphthol (14, 1 mmol), aldehydes (7a–n, 1 mmol), malononitrile (8, 1.0 mmol), and TEACB (5, 2 mol%).

\(^c\)All compounds are known and their structures were established from their spectral data and melting points as compared with authentic samples or literature values.

\(^d\)Simple trituration of the reaction mixture in water and its subsequent filtering afforded essentially pure solid 15a–h.
under the optimized conditions mentioned above (Scheme 4). The results are summarized in Table 4. In addition to the aromatic aldehydes 7a–k, the reaction was also proceeded smoothly using heterocyclic aldehydes 7l–m in high to excellent yields (Entries 9-10, Table 4).

In addition to the enolizable compounds such as 2-hydroxynaphthalene-1,4-dione, 4-hydroxycoumarin, and resorcinol, 2-naphthol (14) was also used in the synthesis of corresponding 2-amino-4H-pyran derivatives containing fused aromatic rings (15a–h) under ball milling under the optimized conditions (Scheme 5). The results are summarized in Table 5.

The mechanism suggested in Scheme 7 seems to be reasonable for the one-pot three-component reaction of phenolic compounds 6, 10, 12 or 14, aldehydes 7, and malononitrile (8) catalyzed by TEACB (5) under solvent-free conditions using the ball milling technique. The first step includes the formation of cyanocinnammonitrile intermediate V from the reaction between aldehyde 7 and malononitrile (8). Then, Michael addition of the phenolic compounds 6, 10, 12, or 14 (intermediate VI) on this intermediate and subsequent cyclization and tautomerization of the next intermediates VII and VIII, respectively, in the presence of TEACB (5), afford the desired product (9, 11, 13, or 15). It is noteworthy that all the above steps can also be competitively catalyzed through weaker hydrogen bonding interactions of the carbamoyl moiety of TEACB (5) with the substrates and reaction intermediates rather than proton transfer from the carboxylic acid functional group of intermediate II.

Finally, to demonstrate the efficiency and capability of the present protocol in the synthesis of different 2-amino-4H-pyran derivatives, it has been compared with some of the previously reported and published procedures. Summarized results in Table 6 clearly show that the present protocol is indeed superior to several of the others in terms of the product yield, reaction time, elimination of solvent, and the required reaction temperature.

**Conclusions**

In conclusion, the use of TEACB, as a bifunctional organocatalyst, was demonstrated for the clean and rapid synthesis of a wide range of 2-amino-3-cyano-4H-pyran derivatives under solvent-free conditions at ambient temperature using the ball milling technique. This new method offers the following competitive advantages: (i) avoiding the use of any transition-metal, corrosive catalyst, and toxic or volatile solvent, (ii) the use of ambient

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**Scheme 6.** A plausible mechanism for the one-pot three-component reaction of enolic components 6, 10, 12 or 14, aldehydes 7 and malononitrile (8) catalyzed by TEACB (5) under solvent-free conditions using the ball milling technique.

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**Table 6.** Comparative synthesis of compounds 9f and 13a using the reported methods versus the present method.

| Entry | Catalyst | Catalyst loading (mol%) | Conditions | Temp. (°C) | Time (min) | Yield (%) | OF (h$^{-1}$) | Reference |
|-------|----------|-------------------------|------------|------------|------------|-----------|-------------|-----------|
| 1     | Tetrabutylammonium fluoride$^a$ | 10 | H$_2$O | Reflux | 30 | 97 | 19.4 | (76) |
| 2     | DABCO$^a$ | 10 | H$_2$O | Reflux | 120 | 89 | 4.5 | (77) |
| 3     | Et$_3$N$^a$ | 10 | CH$_3$CN | r.t | 1440 | 82 | 0.35 | (78) |
| 4     | 2-hydroxyethylammonium formate$^a$ | 2.7 | Ionic liquid | r.t | 10 | 93 | 200 | (79) |
| 10    | TEACB$^b$ | 2 | Ball milling | Ambient | 6 | 97 | 485.0 | This work |
| 6     | Glycine$^b$ | 15 | H$_2$O | 30 | 16 | 92 | 22.7 | (80) |
| 7     | POPINO$^b$ | 10 | H$_2$O | Reflux | 15 | 92 | 36.8 | (10–12) |
| 8     | - | - | TFE | Reflux | 300 | 95 | - | (73) |
| 9     | POP$^b$ | 5 | Ball milling | Ambient | 15 | 98 | 74.8 | (9) |
| 10    | TEACB | 2 | Ball milling | Ambient | 5 | 98 | 590.0 | This work |

$^a$Obtained results for the synthesis of compound 9f.

$^b$Obtained results for the synthesis of compound 13a.
temperature, (iii) ease of product and catalyst purification/isolation by aqueous work-up, (iv) no side reaction, and (v) low costs and simplicity in process and handling.

**Experimental Section**

**General**

All commercially available chemicals were obtained from Merck and Aldrich, and used without further purifications, except for benzaldehyde, which was used as a freshly distilled sample. The ball mill was a Retsch MM 400 swing mill with its 3D-driving of the balls. Two stainless steel balls with 12 mm diameter were used, and the milling frequency was at 28 Hz and the ambient temperature. Analytical thin layer chromatography (TLC) was performed using Merck 0.2 mm silica gel 60 F-254 Al-plates. Melting points, which are uncorrected, were determined using an Electrothermal 9100 apparatus. $^1$H NMR (500 MHz) and $^{13}$C NMR (125 MHz) spectra were recorded on a Bruker DRX-500 Avance spectrometer in CDCl$_3$, as a solvent, at ambient temperature. All chemical shifts are given relative to tetramethylsilane. Infrared (IR) spectra were acquired on a Shimadzu FT-IR8400S spectrometer. All yields refer to the isolated products.

**Preparation of TEACB (5)**

To a 25 mL round-bottomed flask equipped with a magnetic stirrer and a condenser, phthalimide (6.80 mmol, 1.00 g) and tetraethylammonium hydroxide were added (6.80 mmol, 20% w/w in water, $d = 1.01$ g/mL, 5.0 mL). The mixture was stirred at room temperature for 5 min. To this was added 5 mL of distilled water and the mixture was refluxed for 4 h and then allowed to cool. The solvent was evaporated and the residue was kept at 0–4 °C for 1 h to afford pure TEACB (5) in quantitative yield. The white crystals were collected and dried under reduced pressure. Mp 86–88 °C; IR (KBr): $\tilde{\nu}$ 3465, 3340, 3244, 3127, 2192, 1645, 1514, 1406, 1346, 1155 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.87 (s, 1H, C$_3$H$_{benzylic}$), 6.41 (s, 1H, Ar-H), 6.52–6.51 (d, J = 5.0 Hz, 1H, Ar–H), 6.82–6.81 (d, J = 5.0 Hz, 1H, Ar–H), 7.02 (s, 2H, NH$_2$), 7.46–7.45 (d, J = 5.0 Hz, 2H, Ar–H), 8.19–8.18 (d, J = 5.0 Hz, 2H, Ar–H), 9.80 (s, 1H, OH) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 56.0, 103.3, 113.2, 113.5, 121.2, 124.8, 129.5, 130.8, 147.2, 149.8, 154.6, 158.4 161.3 ppm.

**General procedure for the preparation of 2-amino-4H-pyran derivatives (9, 11, 13, or 15)**

A clean and dry 10 mL ball mill vessel with two stainless steel balls was charged with malononitrile (8, 1.0 mmol), aromatic aldehydes (7) (1 mmol), enolic or phenolic components (6, 10, 13, or 16) (1 mmol), and TEACB (5) (2 mol%). The vessel was closed, and the milling was started at ambient temperatures and a speed of 28 Hz for the specific times indicated in Tables 2–5 until products (9, 11, 13, or 15) were formed completely. The reaction progress was monitored by TLC. After completion of the reaction, the product was triturated in a 10 mL beaker containing 5 mL of water for 5 min. The obtained solid was filtered on a Buchner funnel and dried at 80 °C to afford the pure products. The filtrate was evaporated to dryness under reduced pressure, and then EtOH (1 mL) was added. TEACB (5) was filtered off and dried in an oven at 75 °C for the subsequent experiments.

**Analytical data for 2-amino-3-cyano-7-hydroxy-4-(4-nitrophenyl)-4H-chromene (13e):** Mp 232–234 °C; IR (KBr): $\tilde{\nu}$ 3462, 3356, 3206, 3083, 2190, 1645, 1514, 1406, 1346, 1155 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.87 (s, 1H, C$_3$H$_{benzylic}$), 6.41 (s, 1H, Ar–H), 6.52–6.51 (d, J = 5.0 Hz, 1H, Ar–H), 6.82–6.81 (d, J = 5.0 Hz, 1H, Ar–H), 7.02 (s, 2H, NH$_2$), 7.46–7.45 (d, J = 5.0 Hz, 2H, Ar–H), 8.19–8.18 (d, J = 5.0 Hz, 2H, Ar–H), 9.80 (s, 1H, OH) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 56.0, 103.3, 113.2, 113.5, 121.2, 124.8, 129.5, 130.8, 147.2, 149.8, 154.6, 158.4 161.3 ppm.

**Analytical data for 2-amino-3-cyano-7-hydroxy-4-phenyl-4H-chromene (13g):** Mp 229–231 °C; IR (KBr): $\tilde{\nu}$ 3496, 3427, 3334, 2189, 1649, 1406 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.62 (s, 1H, C$_3$H$_{benzylic}$), 6.42–6.41 (d, J = 5.0 Hz, 1H, Ar–H), 6.52–6.48 (d, J = 5.0 Hz, 1H, Ar–H), 6.81–6.80 (d, J = 5.0 Hz, 1H, Ar–H), 6.86 (s, 2H, NH$_2$), 7.18–7.17 (d, J = 5.0 Hz, 2H, Ar–H), 7.22–7.21 (d, J = 5.0 Hz, 1H, Ar–H), 7.32–7.31 (t, 2H, Ar–H), 9.61 (s, 1H, OH) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 57.2, 103.0, 113.7, 114.6, 121.5, 127.5, 128.2, 129.4, 130.8, 147.2, 149.7, 157.9, 161.1 ppm.

**Analytical data for 3-amino-1-(3-nitrophenyl)-1H-benzo[f]chromene-2-carbonitrile (15e):** Mp 230–232 °C; IR (KBr): $\tilde{\nu}$ 3462, 3356, 3206, 3083, 2190, 1645, 1583, 1520, 1472, 1409, 1348, 1231, 1217 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.17 (s, 1H, C$_3$H$_{benzylic}$), 6.64–6.63 (d, J = 5.0 Hz, 2H, Ar–H), 6.89(s, 2H, Ar–H), 6.98–6.97 (d, J = 5.0 Hz, 1H, Ar–H), 7.17 (s, 2H, NH$_2$), 7.40–7.39 (d, J = 5.0 Hz, 1H, Ar–H), 7.48–7.42 (f, J = 5.0 Hz, 2H, Ar–H), 7.60–7.57 (t, J = 5.0 Hz, 1H, Ar–H), 7.68–7.67 (d, J = 5.0 Hz, 1H, Ar–H), 7.88–7.86 (d, J = 10.0 Hz, 1H, Ar–H), 7.95–7.93 (d, J = 10.0 Hz, 1H, Ar–H), 8.00–7.98 (d, J = 10.0 Hz, 1H, Ar–H), 8.05–8.04 (d, J = 5.0 Hz, 1H, Ar–H), 9.25 (s, 1H, OH) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 57.8, 115.4, 117.7, 121.0, 122.2, 122.7, 124.3, 128.3, 129.5, 130.8, 130.9, 131.3, 131.7, 134.6, 148.6, 148.8, 160.8 ppm.
Disclosure statement
No potential conflict of interest was reported by the authors.

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