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Isocyanide-Based Multicomponent Reactions: Synthesis of Alkyl-2-(1-(alkylcarbamoyl)-2,2-dicyanoethyl)benzoate and Isochromeno[3,4-b]pyrrole Derivatives

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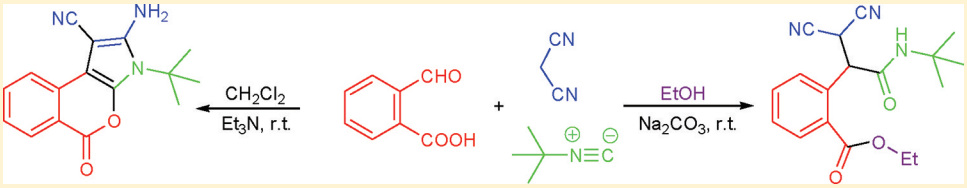
Supporting Information

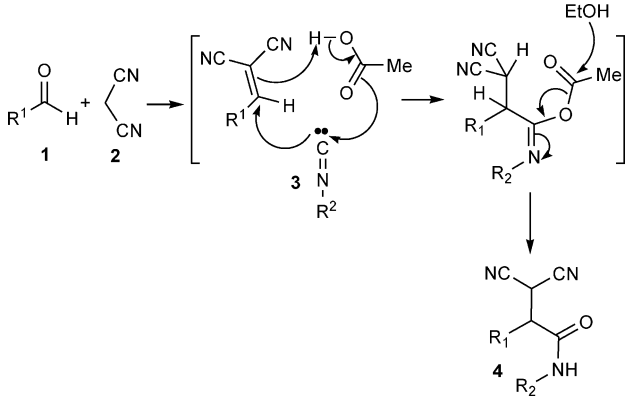


ABSTRACT: A novel four-component reaction between 2-formylbenzoic acids, malononitrile, isocyanides, and alcohols has been developed for a highly efficient preparation of alkyl-2-(1-(alkylcarbamoyl)-2,2-dicyanoethyl)benzoate derivatives. This high atom economy reaction led to the construction of two carbon−carbon bonds, one amide, and one ester group in a single synthetic step. Furthermore, a three-component reaction between 2-formylbenzoic acids, malononitrile, and isocyanides in dichloromethane for the preparation of isochromeno[3,4-b]pyrroles has been reported.

Multicomponent reactions (MCRs) provide unmatched opportunities for the expeditious increase of complexity and diversity in synthetic outcomes. The strategy offers significant advantages over classical stepwise approaches, allowing the formation of several bonds and the construction of complex molecular architectures from simple precursors in a single synthetic operation without the need for isolation of intermediates.[1] The ability of isocyanide to undergo facile α-addition with a nucleophile and an electrophile under mild conditions made it a popular reactant for the development of novel MCRs.[2] As a result of this orthogonal reactivity, MCRs that involve isocyanides are considered as powerful tools in modern organic synthesis as well as in the fields of combinatorial chemistry and drug discovery.[3] Therefore, the design of novel isocyanide-based multicomponent reactions (IMCRs) can be considered as an interesting research topic that also satisfies the practical interest of applied science.[4] As a result, the number of new IMCRs reported in recent years has grown rapidly.[2,4,5] The most versatile of all IMCRs so far is the Ugi four-component condensation (U-4CC) of an acid, an amine, an aldehyde, or a ketone and an isocyanide.[6] The U-4CC is applicable to a broad range of starting materials including bifunctional examples and plays an important role in the isocyanide-based synthesis of organic compounds.

Recently, we described the synthesis of 3,3-dicyano-*N*-alkyl-2-arylpropanamides **4** by a new isocyanide-based multicomponent reaction of aldehydes **1**, malononitrile **2**, isocyanides **3**, and acetic acid in ethanol.[7] In accord with our suggested mechanism, we believe that the reaction could be considered as a special case of the Ugi multicomponent reaction (Scheme 1).

Scheme 1. Synthesis of 3,3-Dicyano-*N*-alkyl-2-arylpropanamides[7]



Herein, we aimed to modify the reaction to make it more convenient and efficient. Since 2-formylbenzoic acid **5** contains both an aldehyde functional group and a carboxylic acid group, it could be used instead of aldehyde and acetic acid in the above reaction. Theoretically, using this substrate could allow us to confirm the role of alcohol in the reaction mechanism. Therefore, we examined the reaction between 2-formylbenzoic acid **5**, malononitrile **2**, isocyanide **3**, and alcohol **6** at room temperature. Gratifyingly, this reaction worked well, leading to the expected product **7** (Scheme 2). In this reaction, the

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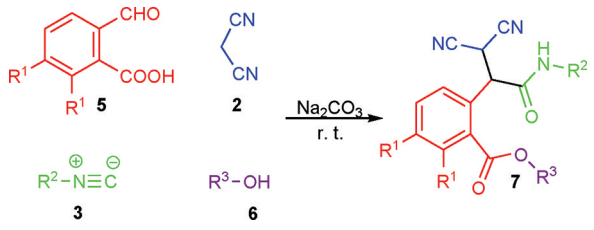
Scheme 2

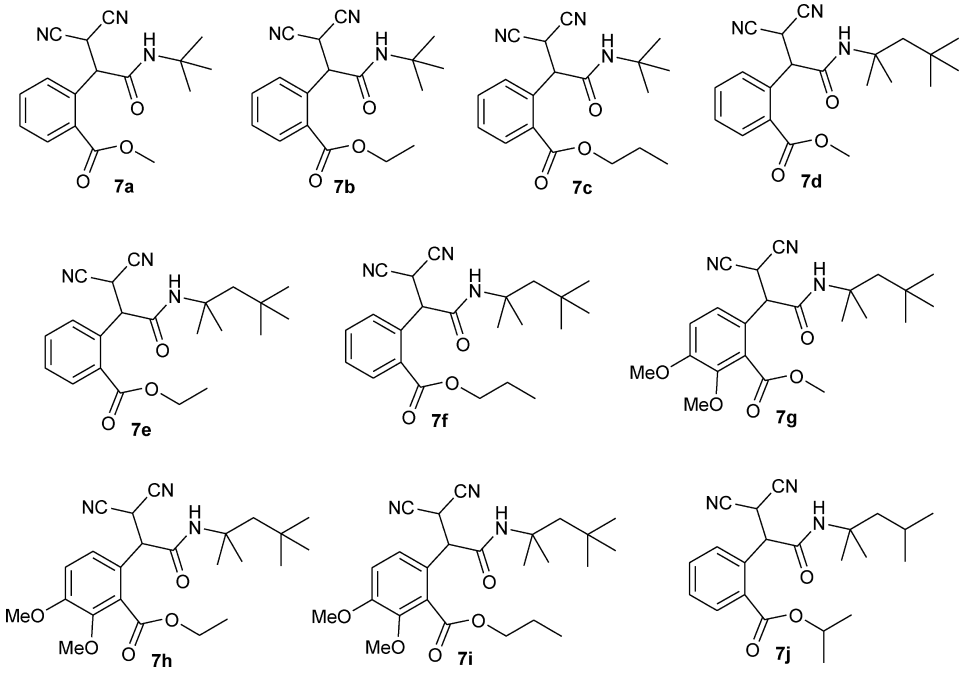


alcohol is not only playing the role of a solvent, but also taking part in the reaction as a reagent.

We chose the reaction of 2-formylbenzoic acid **5**, malononitrile **2**, *tert*-butyl isocyanide **3**, and methanol **6** as a model system for the optimization study. First, several basic and acidic catalysts were examined to set up a standard reaction condition. The experimental results showed that the reaction proceeds promisingly under basic conditions. Then, various basic catalysts such as Na_2CO_3, K_2CO_3, Et_3N, NaOH, and ^tBuOK were examined in the reaction. The results indicated that although K_2CO_3 was found to be effective for this reaction system, the best result was obtained when Na_2CO_3 was utilized as the base. In contrast to Na_2CO_3, the other bases, such as NaOH, Et_3N, NaOH, and ^tBuOK, were not as efficient for this transformation. For instance, when the reaction was performed in the presence of 10 mol % of Na_2CO_3 at room temperature for 5 h, the desired product **7a** was obtained in 86% yield (Table 1, entry 1). Notably, even in the absence of Na_2CO_3 or other additive, **7a** was still produced in 51% yield after 12 h at room temperature. Next, we studied the model reaction catalyzed by Na_2CO_3 (10 mol %) at different temperatures. However, a further increase in the reaction temperature had an adverse effect.

With the optimized conditions established above, we decided to probe the generality of this multicomponent reaction. A variety of starting materials including two formylbenzoic acids (**5**) such as 2-formylbenzoic acid and 5,6-dimethoxy-2-formylbenzoic acid, two isocyanides such as 1,1,3,3-tetrabutyl isocyanide and *tert*-butyl isocyanide, and four different alcohols such as methanol, ethanol, propanol, and *iso*-propanol were tested in this new condensation. Results in Table 1 clearly show that all reactions proceeded smoothly to afford the expected alkyl-2-(1-(alkylcarbamoyl)-2,2-dicyanoethyl)benzoates in good yields. The structure of the products were deduced from their IR, mass, ^1H NMR, and ^{13}C NMR spectra (see the Experimental Section).

Table 1. Synthesis of Alkyl-2-(1-(alkylcarbamoyl)-2,2-dicyanoethyl)benzoate Derivatives[a]



entry	R^1	R^2	R^3	product	yield (%)[b]
1	H	*tert*-butyl	Me	**7a**	86
2	H	*tert*-butyl	Et	**7b**	85
3	H	*tert*-butyl	*n*-pr	**7c**	86
4	H	1,1,3,3-tetramethylbutyl	Me	**7d**	90
5	H	1,1,3,3-tetramethylbutyl	Et	**7e**	87
6	H	1,1,3,3-tetramethylbutyl	*n*-pr	**7f**	84
7	OCH_3	1,1,3,3-tetramethylbutyl	Me	**7g**	90
8	OCH_3	1,1,3,3-tetramethylbutyl	Et	**7h**	93
9	OCH_3	1,1,3,3-tetramethylbutyl	*n*-pr	**7i**	87
10	H	1,1,3,3-tetramethylbutyl	*iso*-pr	**7j**	90

[a]Reaction conditions: 2-formylbenzoic acid **5** (1 mmol), malononitrile **2** (1 mmol), alcohol **6** (2 mL), and Na_2CO_3 (0.1 mmol) were stirred at 70 °C. After 20 min, isocyanide **3** (1 mmol) was added, and the mixture was stirred for 5 h at room temperature. [b]Isolated yield.

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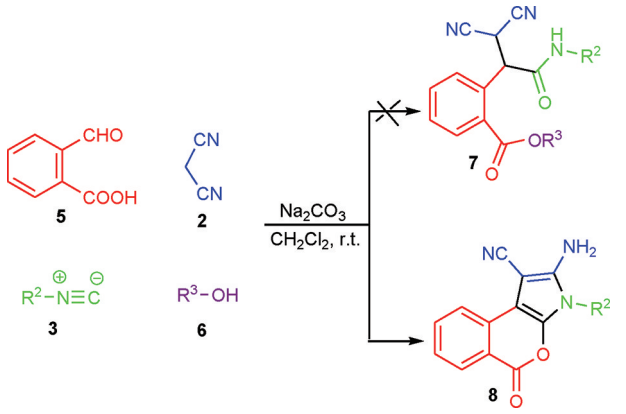
During our investigation, we tried to change the solvent system to utilize alcohol in an equivalent amount. For this aim, we have examined the reaction of alcohols **6** with 2-formylbenzoic acid **5**, malononitrile **2**, and isocyanides **3** in dichloromethane at room temperature in the presence of Na_2CO_3. To our surprise, we found that alcohol was not involved in the reaction, and consequently, the expected product alkyl-2-(1-(alkylcarbamoyl)-2,2-dicyanoethyl)-benzoates **7** was not obtained. Isolation and characterization of the resulted product showed that under this condition, the reaction afforded isochromeno[3,4-b]pyrrole **8** instead (Scheme 3).

Scheme 3

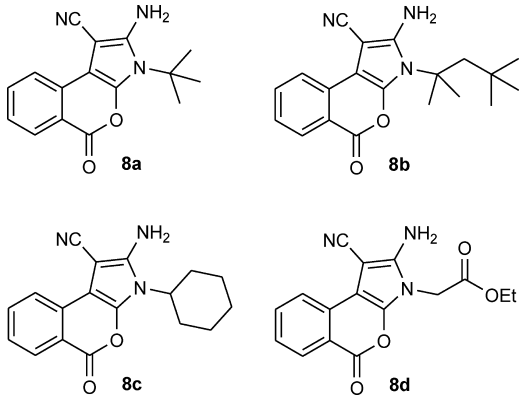


Isocoumarins (isochromens)[8] are an important class of naturally occurring lactones that exhibit a wide range of biological activities such as antimicrobial,[9] antifungal,[10] and antiangiogenic[11] properties and enzyme inhibition.[12] In addition, the isocoumarin ring system is a useful synthetic intermediate for the synthesis of hetero- and carbocyclic compounds including isocarbostyrils, isochromenes, or isoquinolines.[13] Therefore, we focused on examining the efficiency of this new multicomponent reaction by employing a series of different isocyanides, such as cyclohexyl isocyanide, *tert*-butyl isocyanide, and 1,1,3,3-tetramethylbutyl isocyanide, and ethyl isocyanoacetate. It is worth mentioning here that during the optimization of this new reaction, it was found that in contrast to Na_2CO_3, triethylamine (Et_3N) as a basic reagent showed promising results. Therefore, it was decided to employ this reagent for the synthesis of isochromeno[3,4-b]pyrrole derivatives **8**. The results are summarized in Table 2. We found that all reactions proceeded smoothly to afford the expected isochromeno[3,4-b]pyrroles **8** in good yields. The structure of the products were deduced from their IR, mass, ^1H NMR, and ^{13}C NMR spectra (see the Experimental Section).

We have believed that the reaction mechanism is a special case of the Ugi multicomponent reaction. Mechanistically, it is conceivable that the reaction involves the initial formation of the activated alkene, benzylidenemalonodinitrile[14] **9**, through a Knoevenagel condensation of malononitrile **2** and 2-formylbenzoic acid **5**. Intermediate **9** undergoes nucleophilic addition with the isocyanide followed by a nucleophilic attack on the isocyanide by carboxylate to afford the isocoumarin ring **11**. Subsequently, ring-opening of isocoumarin ring by nucleophilic addition of alcohol **6** afforded alkyl-2-(1-(alkylcarbamoyl)-2,2-dicyanoethyl)benzoate derivatives **7** (Scheme 4). When the solvent is dichloromethane, the intermediate **11** undergoes Thorpe–Ziegler intermolecular cyclization into isochromeno-[3,4-b]pyrrole derivates **8**. To clarify the proposed mechanism, first the activated alkene **9** was synthesized by condensation of malononitrile **2** and 2-formylbenzoic acid **5** in the presence Na_2CO_3. Next, the reaction of **9** with the isocyanide and alcohol in the absence of Na_2CO_3 afforded the corresponding alkyl-2-(1-(alkylcarbamoyl)-2,2-dicyanoethyl)benzoate derivatives **7**. It should be noted that the basic catalyst, Na_2CO_3, is required only for the condensation of malononitrile **2** and 2-formylbenzoic acid **5**.

In conclusion, we have developed two new isocyanide-based multicomponent reactions for the synthesis of a wide range of alkyl-2-(1-(alkylcarbamoyl)-2,2-dicyanoethyl)benzoate derivatives and isochromeno[3,4-b]pyrrole derivates from 2-for-

Table 2. Synthesis of Isochromeno[3,4-b]pyrrole Derivatives[a]



entry	R^2	product	yield (%)[b]
1	*tert*-butyl	**8a**	86
2	1,1,3,3-tetramethylbutyl	**8b**	84
3	cyclohexyl	**8c**	92
4	ethyl acetate	**8d**	87

[a]Reaction conditions: 2-formylbenzoic acid **5** (1 mmol), malononitrile **2** (1 mmol), and Et_3N (0.1 mmol) in dichloromethane (2 mL) were stirred at room temperature. After 20 min, isocyanide **3** (1 mmol) was added, and the mixture was stirred for 5 h at room temperature. [b]Isolated yield.

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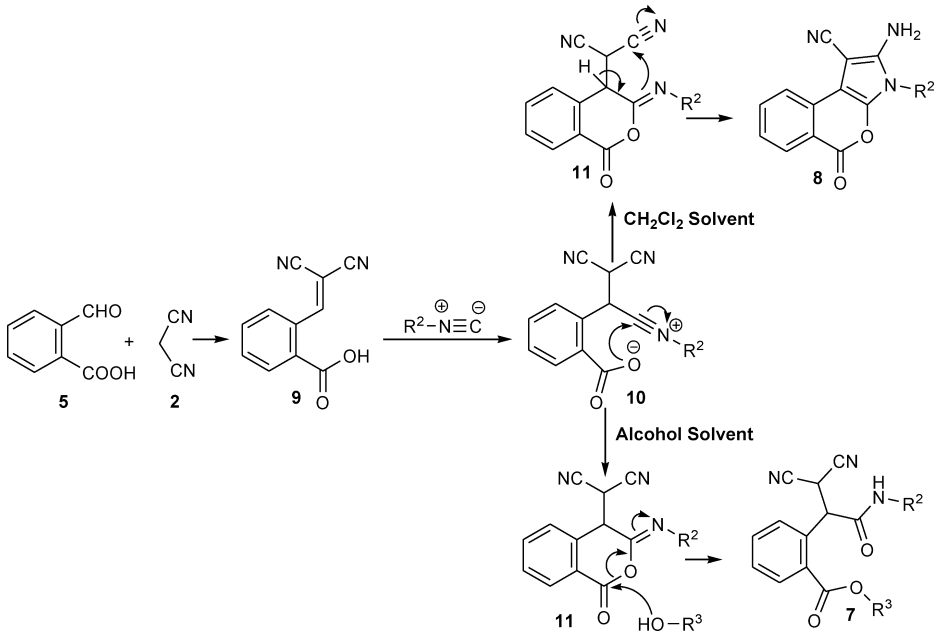
Scheme 4. Proposed Mechanism



mylbenzoic acid, malononitrile, and isocyanides in dichloromethane and alcohol, respectively. These high yielding reactions have been shown to display a good functional group tolerance, while the product isolation is very straightforward. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

EXPERIMENTAL SECTION

General Procedure for Synthesis of Alkyl-2-(1-(alkylcarbamoyl)-2,2-dicyanoethyl)benzoates 7a–i. A solution of 2-formylbenzoic acid (0.15 g, 1 mmol), malononitrile (0.07 g, 1 mmol), alcohol (2 mL), and Na_2CO_3 (0.01 g, 0.1 mmol) was stirred at 70 °C. After 20 min, isocyanide (1 mmol) was added, and the mixture was stirred for 5 h at room temperature. After completion of the reaction as indicated by TLC, the precipitate was filtrated and washed with ether to afford the products.

Methyl 2-(1-(*tert*-Butylcarbamoyl)-2,2-dicyanoethyl)-benzoate (7a). Brown powder (0.27 g, yield 86%): mp 130–132 °C; IR (KBr) (ν_{max}/cm^{-1}) 3349 (NH), 2995, 2962, 2913, 2244 (CN), 2174 (CN), 1694, 1656; MS *m*/*z* 314 (M^+ + 1), 282, 258, 254, 187, 115, 59, 57, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 1.27 (9H, s), 4.00 (3H, s), 4.77 (1H, d, $^3J_{HH}$ = 10.4 Hz), 5.11 (1H, d, $^3J_{HH}$ = 10.4 Hz), 6.81 (1H, brs), 7.42–7.65 (3H, m), 8.00 (1H, d, $^3J_{HH}$ = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 25.4, 28.4, 47.9, 52.0, 53.1, 111.9, 112.2, 127.3, 129.0, 129.7, 131.5, 133.6, 134.8, 166.0, 168.5. Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.13; H, 6.08; N, 13.47.

Ethyl 2-(1-(*tert*-Butylcarbamoyl)-2,2-dicyanoethyl)benzoate (7b). White powder (0.28 g, yield 85%): mp 149–151 °C; IR (KBr) (ν_{max}/cm^{-1}) 3355 (NH), 2983, 2920, 2256 (CN), 1668, 1545; MS, *m*/*z* 328 (M^+ + 1), 282, 272, 229, 143, 115, 57, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 1.27 (9H, s), 1.46 (3H, t, $^3J_{HH}$ = 7.1 Hz), 4.45 (2H, q, $^3J_{HH}$ = 7.1 Hz), 4.77 (1H, d, $^3J_{HH}$ = 10.4 Hz), 5.12 (1H, d, $^3J_{HH}$ = 10.4 Hz), 6.84 (1H, brs), 7.26–7.65 (3H, m), 8.00 (1H, d, $^3J_{HH}$ = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 14.1, 25.3, 28.4, 47.8, 51.9, 62.3, 111.9, 112.2, 127.2, 128.9, 130.0, 131.5, 133.4, 134.7, 166.1, 168.1. Anal. Calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.14; H, 6.41; N, 12.88.

Propyl 2-(1-(*tert*-Butylcarbamoyl)-2,2-dicyanoethyl)-benzoate (7c). Brown powder (0.29 g, yield 86%): mp 100–102 °C; IR (KBr) (ν_{max}/cm^{-1}) 3387 (NH), 2970, 2888, 2256 (CN), 2200 (CN), 1713, 1656, 1530; MS, *m*/*z* 342 (M^+ + 1), 326, 286, 254, 215, 179, 143, 57, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 1.07 (3H, t, $^3J_{HH}$ = 7.4 Hz), 1.27 (9H, s), 1.85 (2H, m), 4.35 (2H, t, $^3J_{HH}$ = 6.7 Hz), 4.78 (1H, d, $^3J_{HH}$ = 10.4 Hz), 5.12 (1H, d, $^3J_{HH}$ = 10.4 Hz), 6.87 (1H, brs), 7.42–7.64 (3H, m), 8.00 (1H, d, $^3J_{HH}$ = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 10.5, 21.9, 25.4, 28.4, 47.8, 52.0, 67.8, 111.9, 112.2, 127.2, 129.0, 130.1, 131.4, 133.4, 134.7, 166.1, 168.2. Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.88; H, 6.83; N, 12.24.

Methyl 2-(1-(2,4,4-Trimethylpentan-2-ylcarbamoyl)-2,2-dicyanoethyl)benzoate (7d). White powder (0.33 g, yield 90%): mp 160–163 °C; IR (KBr) (ν_{max}/cm^{-1}) 3336 (NH), 2964, 2894, 2250 (CN), 1701, 1656, 1562; MS, *m*/*z* 370 (M^+ + 1), 339, 298, 258, 213, 128, 135, 97, 58, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 0.77 (9H, s), 1.31 (3H, s), 1.34 (3H, s), 1.58 (1H, d, $^2J_{HH}$ = 15.0 Hz), 1.72 (1H, d, $^2J_{HH}$ = 15.0 Hz), 4.00 (3H, s), 4.83 (1H, d, $^3J_{HH}$ = 10.7 Hz), 5.10 (1H, d, $^3J_{HH}$ = 10.7 Hz), 6.98 (1H, brs), 7.40–7.64 (3H, m), 7.96 (1H, d, $^3J_{HH}$ = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 25.2, 28.9, 29.2, 31.2, 31.4, 47.9, 51.0, 53.2, 55.9, 111.9, 112.2, 127.1, 129.0, 129.8, 131.3, 133.5, 134.4, 165.3, 168.7. Anal. Calcd for $C_{21}H_{27}N_3O_3$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.22; H, 7.41; N, 11.33.

Ethyl 2-(1-(2,4,4-Trimethylpentan-2-ylcarbamoyl)-2,2-dicyanoethyl)benzoate (7e). White powder (0.33 g, yield 87%): mp 140–143 °C; IR (KBr) (ν_{max}/cm^{-1}) 3305 (NH), 2951, 2882, 2250 (CN), 1701, 1669, 1555; MS, *m*/*z* 384 (M^+ + 1), 338, 312, 272, 255, 227, 149, 97, 58, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 0.77 (9H, s), 1.31 (3H, s), 1.34 (3H, s), 1.46 (3H, t, $^3J_{HH}$ = 7.1 Hz), 1.57 (1H, d, $^2J_{HH}$ = 15.0 Hz), 1.71 (1H, d, $^2J_{HH}$ = 15.0 Hz), 4.45 (2H, q, $^3J_{HH}$ = 7.1 Hz), 4.82 (1H, d, $^3J_{HH}$ = 10.8 Hz), 5.11 (1H, d, $^3J_{HH}$ = 10.8 Hz), 7.01 (1H, brs), 7.39–7.60 (3H, m), 7.98 (1H, d, $^3J_{HH}$ = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 14.1, 25.2, 28.9, 29.1, 31.0, 31.3, 47.9, 51.0, 55.9, 62.4, 111.9, 112.3, 127.0, 128.9, 130.1, 131.3, 133.4, 134.4, 165.4, 168.3. Anal. Calcd for $C_{22}H_{29}N_3O_3$: C, 68.90; H, 7.62; N, 10.96. Found: C, 68.87; H, 7.62; N, 10.91.

Propyl 2-(1-(2,4,4-Trimethylpentan-2-ylcarbamoyl)-2,2-dicyanoethyl)benzoate (7f). Yellow powder (0.33 g, yield 84%): mp 116–118 °C; IR (KBr) (ν_{max}/cm^{-1}) 3317 (NH), 2957, 2907, 2250 (CN), 2193 (CN), 1707, 1669, 1550; MS, *m*/*z* 398 (M^+ + 1), 382, 368, 326, 310, 269, 241, 163, 156, 87, 58, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 0.77 (9H, s), 1.07 (3H, t, $^3J_{HH}$ = 7.4 Hz), 1.31 (6H, s), 1.55–1.87 (4H, m), 4.36 (2H, t, $^3J_{HH}$ = 6.9 Hz), 4.82 (1H, d, $^3J_{HH}$ = 10.5 Hz), 5.11 (1H, d, $^3J_{HH}$ = 10.5 Hz), 7.00 (1H, brs), 7.35–7.59 (3H, m), 7.96 (1H, d, $^3J_{HH}$ = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C

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(ppm) 10.5, 21.9, 25.2, 28.9, 29.1, 31.0, 31.3, 47.9, 51.0, 55.8, 67.9, 111.9, 112.3, 127.1, 128.9, 130.2, 131.2, 133.4, 134.4, 165.4, 168.4. Anal. Calcd for $C_{23}H_{31}N_3O_3$: C, 69.49; H, 7.86; N, 10.57. Found: C, 69.44; H, 7.87; N, 10.62.

Methyl 6-(1-(2,4,4-Trimethylpentan-2-ylcarbamoyl)-2,2-dicyanoethyl)-2,3-dimethoxybenzoate (7g). White powder (0.39 g, yield 90%): mp 141−143 °C; IR (KBr) (ν_{max}/cm^{-1}) 3330 (NH), 2891, 2250 (CN), 1706, 1668, 1551; MS, *m*/*z* 430 (M^+ + 1), 398, 358, 318, 301, 273, 195, 136, 107, 58, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 0.83 (9H, s), 1.36 (3H, s), 1.39 (3H, s), 1.62 (1H, d, $^2J_{HH}$ = 15.0 Hz), 1.75 (1H, d, $^2J_{HH}$ = 15.0 Hz), 3.94 (6H, s), 4.05 (1H, d, $^3J_{HH}$ = 10.5 Hz), 4.10 (3H, s), 5.81 (1H, d, $^3J_{HH}$ = 10.5 Hz), 6.80 (1H, brs), 7.06 (1H, d, $^3J_{HH}$ = 8.7 Hz), 7.12 (1H, d, $^3J_{HH}$ = 8.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm) 24.6, 28.5, 28.6, 30.6, 30.9, 48.7, 50.6, 52.9, 55.5, 55.6, 61.1, 111.5, 112.0, 114.4, 121.8, 123.2, 128.2, 146.7, 152.9, 164.7, 168.5. Anal. Calcd for $C_{23}H_{31}N_3O_5$: C, 64.32; H, 7.27; N, 9.78. Found: C, 64.37; H, 7.33; N, 9.67.

Ethyl 6-(1-(2,4,4-Trimethylpentan-2-ylcarbamoyl)-2,2-dicyanoethyl)-2,3-dimethoxybenzoate (7h). White powder (0.41 g, yield 93%): mp 133−135 °C; IR (KBr) (ν_{max}/cm^{-1}) 3331 (NH), 2289, 2250 (CN), 1700, 1663, 1552; MS, *m*/*z* 444 (M^+ + 1), 412, 398, 372, 332, 315, 287, 209, 156, 107, 58, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 0.77 (9H, s), 1.29 (3H, s), 1.33 (3H, s), 1.45 (3H, $^3J_{HH}$ = 7.1 Hz), 1.57 (1H, d, $^2J_{HH}$ = 15.0 Hz), 1.69 (1H, d, $^2J_{HH}$ = 15.0 Hz), 3.88 (3H, s), 3.89 (3H, s), 4.00 (1H, d, $^3J_{HH}$ = 10.5 Hz), 4.48−4.57 (2H, m), 4.76 (1H, d, $^3J_{HH}$ = 10.5 Hz), 6.75 (1H, brs), 6.99 (1H, d, $^3J_{HH}$ = 8.7 Hz), 7.06 (1H, d, $^3J_{HH}$ = 8.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm) 13.8, 24.6, 28.5, 30.6, 30.9, 48.6, 50.7, 55.5, 55.6, 61.0, 62.2, 111.4, 111.9, 114.3, 121.7, 123.2, 128.6, 146.7, 152.9, 164.7, 168.0. Anal. Calcd for $C_{24}H_{33}N_3O_5$: C, 64.99; H, 7.50; N, 9.47. Found: C, 64.93; H, 7.53; N, 9.46.

Propyl 6-(1-(2,4,4-Trimethylpentan-2-ylcarbamoyl)-2,2-dicyanoethyl)-2,3-dimethoxybenzoate (7i). White powder (0.40 g, yield 87%): mp 129−131 °C; IR (KBr) (ν_{max}/cm^{-1}) 3317 (NH), 2889, 2250 (CN), 1700, 1668, 1554; MS, *m*/*z* 458 (M^+ + 1), 442, 426, 386, 346, 329, 301, 223, 156, 107, 58, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 0.76 (9H, s), 1.05 (3H, $^3J_{HH}$ = 7.4 Hz), 1.29 (3H, s), 1.32 (3H, s), 1.55 (1H, d, $^2J_{HH}$ = 15.0 Hz), 1.69 (1H, d, $^2J_{HH}$ = 15.0 Hz), 1.73−1.92 (2H, m), 3.87 (3H, s), 3.88 (3H, s), 3.99 (1H, d, $^3J_{HH}$ = 10.5 Hz), 4.29−4.50 (2H, m), 4.86 (1H, d, $^3J_{HH}$ = 10.5 Hz), 6.78 (1H, brs), 6.99 (1H, d, $^3J_{HH}$ = 8.7 Hz), 7.09 (1H, d, $^3J_{HH}$ = 8.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm) 9.9, 21.6, 24.6, 28.5, 28.6, 30.6, 30.9, 48.6, 50.6, 55.4, 55.5, 61.0, 67.8, 111.5, 112.0, 114.3, 121.7, 123.3, 128.6, 146.6, 152.9, 164.8, 168.2. Anal. Calcd for $C_{25}H_{35}N_3O_5$: C, 65.62; H, 7.71; N, 9.18. Found: C, 65.65; H, 7.72; N, 9.16.

Isopropyl 2-(1-(2,4,4-Trimethylpentan-2-ylcarbamoyl)-2,2-dicyanoethyl)benzoate (7j). Yellow powder (0.36 g, yield 90%): mp 147−149 °C; IR (KBr) (ν_{max}/cm^{-1}) 3318 (NH), 2953, 2909, 2251 (CN), 2192 (CN), 1711, 1666, 1551; MS, *m*/*z* 398 (M^+ + 1), 382, 368, 326, 286, 269, 239, 163, 156, 87, 58, 41; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H (ppm) 0.83 (9H, s), 1.27 (3H, s), 1.33 (3H, s), 1.34 (6H, d, $^3J_{HH}$ = 6.4 Hz), 1.94−1.96 (2H, m), 4.99−5.12 (3H, m), 7.41−7.95 (5H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C (ppm) 22.0, 26.3, 26.5, 29.0, 29.6, 31.2, 31.6, 48.2, 50.1, 55.0, 69.4, 113.8, 114.0, 128.8, 129.1, 130.5, 131.5, 133.1, 135.9, 166.1, 167.3, 168.7. Anal. Calcd for $C_{23}H_{31}N_3O_3$: C, 69.49; H, 7.86; N, 10.57. Found: C, 69.21; H, 7.95; N, 10.50.

General Procedure for Synthesis of Isochromeno[3,4-b]-pyrroles 8a−d. A solution of 2-formylbenzoic acid (0.15 g, 1 mmol), malononitrile (0.07 g, 1 mmol), and Et_3N (0.01 g, 0.1 mmol) in dichloromethane (2 mL) was stirred at room temperature. After 20 min, isocyanide (1 mmol) was added, and the mixture was stirred for 5 h at room temperature. After completion of the reaction as indicated by TLC, the solvent was evaporated, and the residue was washed with ether and recrystallized in ether/*n*-hexane (1:1) to give pure products.

3-*tert*-Butyl-2-amino-3,5-dihydro-5-oxoisochromeno[3,4-b]-pyrrole-1-carbonitrile (8a). Yellow powder (0.24 g, yield 86%): mp 236−238 °C; IR (KBr) (ν_{max}/cm^{-1}) 3400, 3343 (NH), 2206 (CN), 1713 (C═O), 1612, 1555; MS, *m*/*z* (%) 281 (M^+), 255, 224, 105, 83, 57, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 1.77 (9H, s), 4.22 (1H, brs), 7.35−8.27 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 30.3, 61.6, 69.3, 96.3, 116.9, 117.0, 120.9, 125.9, 131.0, 133.9, 135.5, 138.0, 144.4, 160.5. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.34; H, 5.39; N, 14.91.

2-Amino-3,5-dihydro-3-(2,4,4-trimethylpentan-2-yl)-5-oxoisochromeno[3,4-b]pyrrole-1-carbonitrile (8b). Yellow powder (0.28 g, yield 84%): mp 180−183 °C; IR (KBr) (ν_{max}/cm^{-1}) 3374, 3317, 3248 (NH), 2193 (CN), 1720 (C═O), 1606, 1555; MS, *m*/*z* (%) 337 (M^+), 311, 266, 244, 113, 105, 58, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 0.92 (9H, s), 1.99 (6H, s), 2.15 (1H, s), 4.21 (2H, brs), 7.41−7.84 (2H, m), 8.07 (1H, d, $^3J_{HH}$ = 7.5 Hz), 8.35 (1H, d, $^3J_{HH}$ = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 30.8, 31.4, 31.6, 52.0, 64.7, 64.8, 100.0, 116.9, 121.0, 125.9, 131.0, 133.9, 134.1, 135.5, 144.6, 160.4. Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.23; H, 6.82; N, 12.47.

2-Amino-3-cyclohexyl-3,5-dihydro-5-oxoisochromeno[3,4-b]pyrrole-1-carbonitrile (8c). Yellow powder (0.28 g, yield 92%): mp 238−240 °C; IR (KBr) (ν_{max}/cm^{-1}) 3437, 3336, 3229 (NH), 2206 (CN), 1738 (C═O), 1713, 1612, 1562; MS, *m*/*z* (%) 307 (M^+), 281, 224, 105, 83, 55, 41; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 1.15−2.08 (10H, m), 4.09−4.20 (1H, m), 6.42 (1H, s), 7.32−7.86 (3H, m), 8.11 (1H, d, $^3J_{HH}$ = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 25.1, 25.7, 30.9, 54.3, 61.5, 95.0, 116.6, 118.2, 120.0, 125.8, 131.3, 134.5, 136.2, 137.1, 146.1, 160.3. Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.33; H, 5.55; N, 13.69.

Ethyl 2-(2-Amino-1-cyano-5-oxoisochromeno[3,4-b]pyrrol-3(5*H*)-yl)acetate (8d). Yellow powder (0.27 g, yield 87%): mp 219−222 °C; IR (KBr) (ν_{max}/cm^{-1}) 3425, 3343, 3229 (NH), 2206 (CN), 1738, 1713 (C═O), 1618; MS, *m*/*z* (%) 311 (M^+), 285, 266, 224, 191, 105, 45, 29; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm) 1.35 (3H, $^3J_{HH}$ = 7.1 Hz), 4.14 (1H, s), 4.30 (3H, $^3J_{HH}$ = 7.1 Hz), 4.72 (2H, s), 7.36−7.80 (2H, m), 7.98 (1H, d, $^3J_{HH}$ = 7.8 Hz), 8.25 (1H, d, $^3J_{HH}$ = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 14.1, 43.0, 62.9, 69.8, 95.8, 116.1, 117.5, 121.0, 126.1, 131.5, 134.1, 135.8, 136.5, 143.0, 160.4, 167.3. Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.77; H, 4.20; N, 13.47.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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