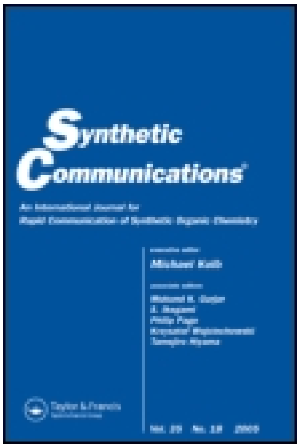

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# Isocyanide-Catalyzed Reaction of Tetracyanoethylene and Activated 1,3-Dicarbonyl CH-Acid Compounds: A Rapid and Efficient Synthesis of Pyran Annulated Heterocyclic Systems

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# Isocyanide-Catalyzed Reaction of Tetracyanoethylene and Activated 1,3-Dicarbonyl CH-Acid Compounds: A Rapid and Efficient Synthesis of Pyran Annulated Heterocyclic Systems

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**Abstract:** An isocyanide-catalyzed reaction between tetracyanoethylene and various activated CH-acid compounds to afford the corresponding pyran annulated heterocyclic ring systems, in high yield at room temperature within a few minutes, is described. To the best of our knowledge, this is the first example in which isocyanide functions as only a catalyst but not a reagent.

**Keywords:** CH-acid, isocyanide-catalyzed reaction, pyrans, tetracyanoethylene

## INTRODUCTION

Pyrans and their derivatives are of considerable interest because of their wide range of biological properties,[1] such as spasmolytic, diuretic, anticoagulant, and anti-cancer, anti-anaphylactic activity.[2–6] In addition, they can be used as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS-associated dementia, and

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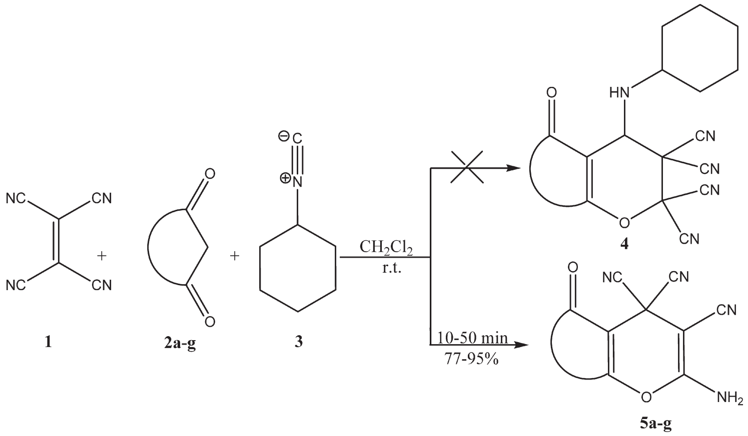


*Scheme 1.*

Down syndrome, as well as for the treatment of schizophrenia and myoclonus.[7] 4*H*-Pyrans also constitute the structural unit of a series of natural products.[8,9]

In view of our general interest in isocyanide-based multicomponent reactions (MCRs) involving zwitterionic species,[10] we were intrigued by the possibility trapping of the 1,3-zwitterionic intermediate generated from isocyanide and tetracyanoethylene (TCNE) with activated CH-acids. We did not observe the expected MCR product **4**; instead, the reaction afforded the corresponding pyran annulated heterocyclic systems (PAHS) with isocyanide playing a catalyst role in the reaction between TCNE and activated CH-acids. To the best of our knowledge, an isocyanide-catalyzed reaction is not known (Scheme 1).

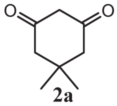
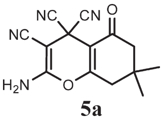
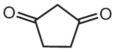
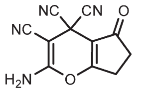
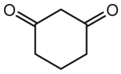
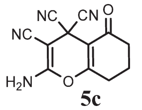
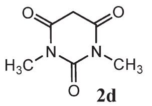
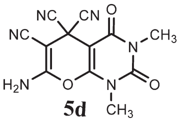
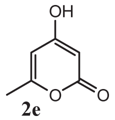
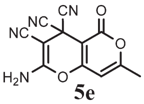
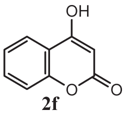
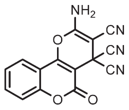
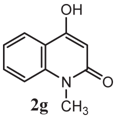
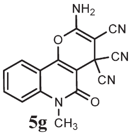
## RESULTS AND DISCUSSION

In an initial experiment, the reaction of TCNE **1** with 5,5-dimethylcyclohexane-1,3-dione **2** in the presence of cyclohexyl isocyanide **3** (10 mol%) in $CH_2Cl_2$ afforded the **2**-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxochromene-3,4,4-tricarbonitrile **5a** in 89% yield. Similar reactivity was observed with other cyclic-1,3-dicarbonyl compounds such as cyclopentane-1,3-dione and cyclohexane-1,3-dione, and results are summarized in Table 1.

All of the products are new compounds that were characterized by IR, $^1$H NMR, and $^{13}$C NMR spectra. The mass spectra of products displayed molecular ion peaks at the appropriate m/z values.

The $^1$H NMR spectrum of **5a** exhibited three singlets identified as one methyl (at $\delta = 1.04$ ppm) and two methylene (at $\delta = 2.44$ and 2.59 ppm)

***Table 1.*** Reaction of TCNE with various β-dicarbonyl activated CH-acids in the presence of a catalytic amount of cyclohexyl isocyanide

| Entry | CH-acid | Product | Yield (%) | Time (min) |
|---|---|---|---|---|
| 1 |  **2a** |  **5a** | 89 | 30 |
| 2 |  **2b** |  **5b** | 95 | 10 |
| 3 |  **2c** |  **5c** | 90 | 30 |
| 4 |  **2d** |  **5d** | 79 | 40 |
| 5 |  **2e** |  **5e** | 82 | 20 |
| 6 |  **2f** |  **5f** | 84 | 15 |
| 7 |  **2g** |  **5g** | 84 | 50 |

protons. The $NH_2$ protons resonate at $\delta = 8.40$ ppm. The $^1H$ decoupled $^{13}C$ NMR spectrum of **5a** showed 12 distinct resonances, in agreement with the suggested structures.

To illustrate the role of isocyanide, the reaction of TCNE **1** and 5,5-dimethylcyclohexane-1,3-dione **2** was studied in the absence of cyclohexyl isocyanide. Only a trace yield of the desired product was obtained under similar conditions after 30 min.

The reaction of 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione with TCNE **1** in the presence of isocyanide in $CH_2Cl_2$ at room temperature also afforded similar pyran annulated heterocyclic systems (Table 1, entry 4).

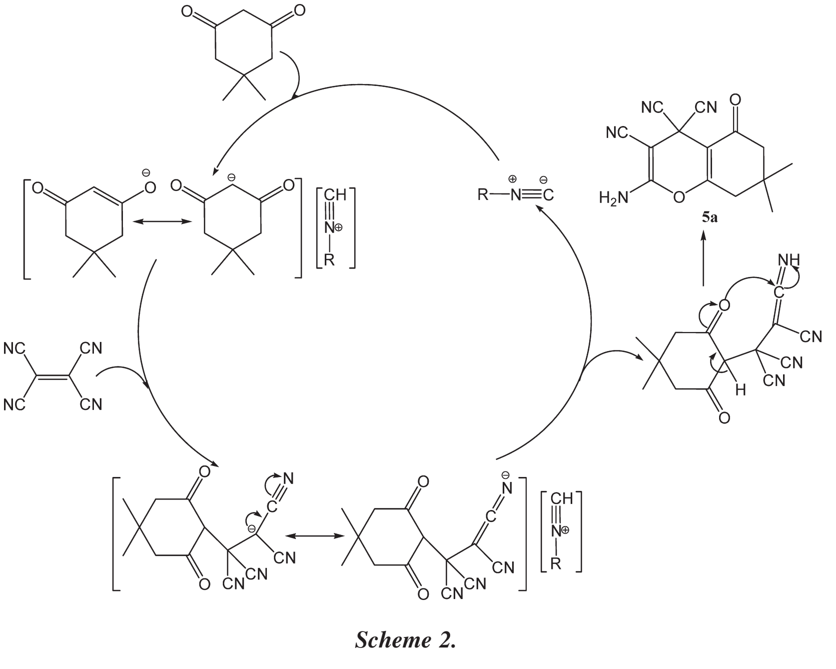
In view of the success of these reactions, we explored the use of 4-hydroxy-6-methyl-2*H*-pyran-2-one, 4-hydroxy-2*H*-chromen-2-one, and 4-hydroxy-1-methylquinolin-2(1*H*)-one as activated CH-acid in this reaction. Treatment of 4-hydroxy-6-methyl-2*H*-pyran-2-one, 4-hydroxy-2*H*-chromen-2-one, or 4-hydroxy-1-methylquinolin-2(1*H*)-one with TCNE **1** in the presence of isocyanide in $CH_2Cl_2$ at room temperature led to the formation of the corresponding pyran annulated heterocyclic systems in high yields (Table 1, entries 5–7).

A mechanistic rationalization for the reaction is provided in Scheme 2.

In conclusion, we have devised a rapid and very efficient isocyanide-catalyzed approach for the synthesis of pyran annulated heterocyclic ring systems under neutral and mild reaction conditions with excellent yields. To the best of our knowledge, this is the first example in which isocyanide functions as only a catalyst, but not a reagent.

## EXPERIMENTAL

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. $^1$H and $^{13}$C NMR spectra were recorded on a



*Scheme 2.*

Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz. $^1$H and $^{13}$C NMR spectra were obtained on solutions in $CDCl_3$ and DMSO-$d_6$.

## Typical Experimental Procedure: Preparation of 2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxochromene-3,4,4-tricarbonitrile (5a)

A mixture of cyclohexyl isocyanide (0.011 g, 10 mol%) in $CH_2Cl_2$ (2 mL) was added dropwise to a magnetically stirred solution of tetracyanoethylene (0.128 g, 1.0 mmol) and 5,5-dimethylcyclohexane-1,3-dione (0.140 g, 1.0 mmol) in $CH_2Cl_2$ (15 mL) at room temperature and was stirred for 30 min. After completion of the reaction, the solvent was removed under vacuum, and the residue was crystallized from $CH_2Cl_2$/n-hexane 1:2 to yield 0.238 g of **5a** as a pink powder (89%). Mp 198–200°C. IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3370, 3345 ($NH_2$), 2209 (CN), 1681 (C=O). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 1.04 (s, 6H, $2CH_3$), 2.44 (s, 2H, $CH_2$), 2.59 (s, 2H, $CH_2$), 8.40 (s, 2H, $NH_2$). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_C$ (ppm) 13.76, 18.58, 27.18, 30.07, 31.77, 49.69, 101.91, 113.74 (CN), 116.16 (CN), 158.83, 166.36, 193.94 (C=O). MS, *m/z* (%): 268 (M$^+$, 20), 242 (40), 226 (100), 185 (55), 157 (30), 129 (35), 83 (45), 57 (50), 41 (60). Anal. calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.50; H, 4.45; N, 20.69.

## Data

2-Amino-6,7-dihydro-5-oxocyclopenta[b]pyran-3,4,4(5H)-tricarbonitrile (**5b**)

Cream powder (0.215 g, 95%): mp 178–180°C. IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3382, 3360 ($NH_2$), 2201 (CN), 1666 (C=O). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 2.61 (br, 2H, $CH_2$), 2.84 (br, 2H, $CH_2$), 8.60 (s, 2H, $NH_{2).}$ $^{13}$C NMR (75 MHz, DMSO-$d_6$) δc 19.06, 29.43, 33.69, 49.26, 105.46, 113.09 (CN), 116.68 (CN), 161.08, 180, 198.85 (C=O). MS, *m/z* (%): 226 (M$^+$, 30), 200 (25), 184 (20), 78 (20), 57 (60), 41(100). Anal. calcd. for $C_{11}H_6N_4O_2$: C, 58.41; H, 2.67; N, 24.77. Found: C, 58.27; H, 2.58; N, 23.92.

2-Amino-5,6,7,8-tetrahydro-5-oxochromene-3,4,4-tricarbonitrile (**5c**)

Pink powder (0.216 g, 90%): mp 196–198°C. IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3372, 3355 ($NH_2$), 2208 (CN), 1668 (C=O). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 1.99 (br, 2H, $CH_2$), 2.49 (br, 2H, $CH_2$), 2.64 (br, 2H, $CH_2$), 8.36 (s, 2H, $NH_2$). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_C$ (ppm) 19.53, 27.40, 30.71, 35.92, 50.29, 103.10, 114.37 (CN), 116.67 (CN), 159.13, 168.83, 194.58 (C=O). MS, *m/z* (%): 240 (M$^+$, 25), 214 (100), 184 (90), 158 (40), 120 (35), 88 (30), 66 (65), 39 (85). Anal. calcd. for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32. Found: C, 60.10; H, 3.32; N, 23.14.

6-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrano[3,2-d]pyrimidine-7,8,8-tricarbonitrile (**5d**)

Light green powder (0.224 g, 79%): mp 210°C (dec). IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3351, 3340 ($NH_2$), 2214 (CN), 1718 (C=O), 1685 (C=O). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta_H$ (ppm) 3.23 (s, 3H, $CH_3$), 3.29 (s, 3H, $CH_3$), 8.67 (s, 2H, $NH_2$). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta_C$ (ppm) 28.48, 30.02, 32.08, 50.28, 78.75, 114.07 (CN), 116.23 (CN), 149.72, 152.94, 158.81 (C=O), 159.62 (C=O). MS, $m/z$ (%): 268 ($M^+ - 16$, 20), 242 (25), 209 (30), 181 (20), 154 (70), 132 (25), 105 (60), 78 (60), 56 (100), 41 (75). Anal. calcd. for $C_{12}H_8N_6O_3$: C, 50.71; H, 2.84; N, 29.57. Found: C, 50.13; H, 2.75; N, 29.32.

2-Amino-7-methyl-5-oxopyrano[4,3-b]pyran-3,4,4(5H)-tricarbonitrile (**5e**)

Cream powder (0.208 g, 82%): mp 203°C (dec). IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3382, 3366 ($NH_2$), 2215 (CN), 1729 (C=O). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta_H$ (ppm) 2.33 (s, 3H, $CH_3$), 6.48 (s, 1H, olefin), 8.52 (s, 2H, $NH_2$). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta_C$ (ppm) 20.06, 31.70, 49.77, 89.38, 98.94, 113.53 (CN), 116.63 (CN), 159.30, 160.15, 160.68, 167.72 (C=O). MS, $m/z$ (%): 228 ($M^+ - 26$, 20), 200 (25), 85 (95), 69 (30), 43 (100). Anal. calcd. for $C_{12}H_6N_4O_3$: C, 56.70; H, 2.38; N, 22.04. Found: C, 56.35; H, 2.23; N, 21.89.

2-Amino-5-oxopyrano[3,2-c]chromene-3,4,4(5H)-tricarbonitrile (**5f**)

White powder (0.244 g, 84%): mp 220°C (dec). IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3355, 3345 ($NH_2$), 2213 (CN), 1712 (C=O). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta_H$ (ppm) 7.60–7.87 (m, 4H, arom), 8.69 (s, 2H, $NH_2$). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta_C$ (ppm) 32.19, 50.03, 92.49, 112.57 (CN), 113.48 (CN), 116.52, 117.55, 123.78, 125.86, 135.71, 153.14, 156.43, 158.69, 159.10 (C=O). MS, $m/z$ (%): 264 ($M^+ - 26$, 35), 236 (20), 150 (40), 121 (100), 92 (35), 65 (20), 45 (20). Anal. calcd. for $C_{15}H_6N_4O_3$: C, 62.07; H, 2.08; N, 19.3. Found: C, 61.33; H, 2.09; N, 19.02.

2-Amino-5,6-dihydro-6-methyl-5-oxopyrano[3,2-c]quinoline-3,4,4-tricarbonitrile (**5g**)

White powder (0.254 g, 84%): mp 219°C (dec). IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3375, 3360 ($NH_2$), 2203 (CN), 1676 (C=O). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta_H$ (ppm) 3.69 (s, 3H, $CH_3$), 7.45–7.96 (m, 4H, arom), 8.53 (s, 2H, $NH_2$). $^{13}$C

NMR (75 MHz, DMSO-$d_6$) $\delta_C$ (ppm) 30.22, 32.57, 50.34, 96.56, 112.09 (CN), 114.27 (CN), 116.07, 116.95, 123.46, 123.55, 134.40, 140.00, 152.20, 158.59, 159.52 (C=O). MS, $m/z$ (%): 304 ($MH^+$, 10), 285 (50), 276 (100), 249 (40), 150 (30), 104 (30), 84 (25), 49 (70). Anal. calcd. for $C_{16}H_9N_5O_2$: C, 63.37; H, 2.99; N, 23.09. Found: C, 62.09; H, 2.87; N, 22.05.

## ACKNOWLEDGMENT

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