Simple Synthesis of 3-Oxopropanenitriles *via* Electrophilic Cyanoacetylation of Heterocycles with Mixed Anhydrides

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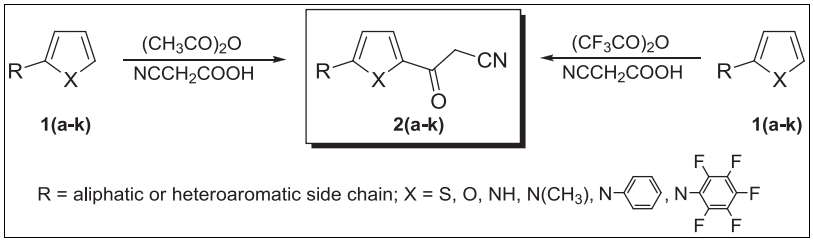

A simple and efficient method for the synthesis of 3-oxopropanenitriles from variously substituted heterocyclic compounds *via* direct electrophilic cyanoacetylation is described. A series of heterocyclic 3-oxopropanenitriles **2**(**a**–**k**) have been synthesized using mixed anhydride (acetic or trifluoroacetic anhydride:cyanoacetic acid) in the presence of $Mg(ClO_4)_2{\cdot}2H_2O$ as catalyst. This method can be extended also for the cyanoacetylation of electron poor aromatic compounds.

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INTRODUCTION

Substituted 3-oxopropanenitriles are versatile synthetic intermediates or reactants with a great interest in organic chemistry. Suitably situated keto- and cyano- strong electron withdrawing groups are favorable for reactions with common bidentate reagents to form a variety of heterocyclic compounds possessing biological and pharmaceutical activities [1]. Moreover, because of the presence of active hydrogen on C-2, these compounds can participate in a variety of condensation and substitution reactions. Recently, using 3-oxopropanenitriles as starting materials, the synthesis of different heterocycles and their derivatives such as pyrazoles, 4-cyano pyrroles, pyridines, isoxazoles, pyrimidines, pyridazines, pyrans, thiazoles, π-conjugated thiophene derivatives, and optically active β-hydroxy carboxylic nitriles has been reported [2]. Because most of these heterocycles are potentially bioactive materials, facile synthetic procedures for the preparation of 3-oxopropanenitriles are needed.

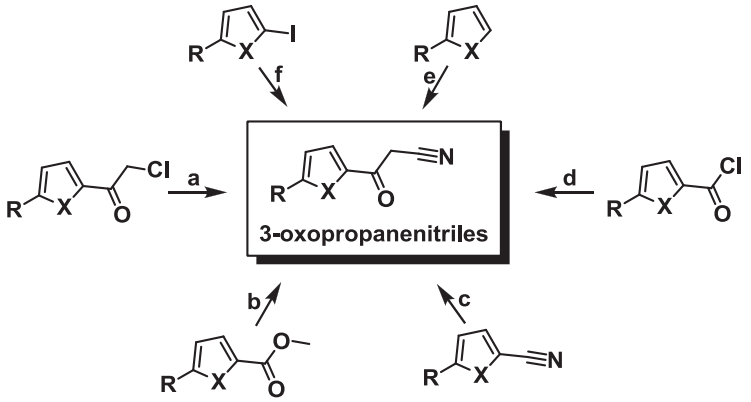
Several synthetic pathways for the preparation of 3-oxopropanenitriles are present in literature (Scheme 1). The oldest method involves the reaction of α-haloketones with cyanide [3], while the classical method uses the Claisen type reaction [4] of appropriate aromatic or heteroaromatic esters with *in situ* generated metallated nitriles. The synthesis of 3-oxopropanenitriles can be accomplished also by the Guareshi–Thorpe condensation of aromatic or heteroaromatic nitriles with acetonitrile in the presence of bulky bases [5]. Another approach is the acylation of an acid chloride with the lithium salt of cyanoacetic acid [6]. The straightforward electrophilic substitution of nitrogen containing heteroaromatic compounds (indoles, pyrroles) with cyanoacetic acid in acetic anhydride was discovered for the first time in 2004 [7]. The synthesis of 3-oxopropanenitrile by using a mixed anhydride from cyanoacetic acid–acetic anhydride mixture with electron rich aromatics in presence of indium trichloride as a Lewis acid was described by Elnagdi *et al* [8].

Recently, several new methods have been developed, such as indium-mediated coupling of bromoacetonitriles with acyl cyanides or palladium-catalyzed carbonylation of aryl iodides and trimethylsilylacetonitrile [9]. In all cases, these synthetic methods are strictly exploitable for electron-rich aromatic compounds, and additional synthetic steps for the preparation of the starting materials are needed.

In this work we report the preparation of 3-oxopropanenitriles by direct cyanoacetylation of different heterocycles, including electron poor aromatic compounds, with mixed anhydride (cyanoacetic acid:acetic anhydride or cyanoacetic acid:trifluoroacetic anhydride) in the presence of $Mg(ClO_4)_2{\cdot}2H_2O$ as catalyst, using commercially available starting materials.

The present study was initiated because of the continuous growing demand of heteroaromatic 3-oxopropanenitriles, used as starting materials for the Vilsmeier-Haack Arnold haloformylation. Our study was focused on the introduction of 3-oxopropanenitriles on electron reach and electron poor heterocycles, such as furan, thiophene, pyrrole, and their derivatives.

Scheme 1. Known synthetic approaches towards 3-oxopropanenitriles.



X = CH=CH or heteroatom (S, O, NH, etc.)
R = H, aliphatic or heteroaromatic side chain

a) NaCN or KCN, MeOH/H_2O (3:1); **b)** CH_3CN, NaH, THF; **c)** CH_3CN, *t*-BuOH, NaH, Et_2O; **d)** $NCCH_2COOH$, *n*-BuLi, THF; **e)** $(CH_3CO)_2O$, $NCCH_2COOH$, $InCl_3$, xylene; **f)** $(CH_3)_3SiCH_2CN$, $\{(2\text{-Me-allyl})PdCl\}_2$, $CuBr_2$, ZnF_2, CO, DMF.

RESULTS AND DISCUSSION

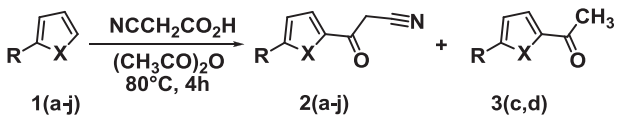
The heteroaromatic 3-oxopropanenitriles used in our research were prepared by using two different types of mixed anhydrides: cyanoacetic acid:acetic anhydride or cyanoacetic acid:trifluoroacetic anhydride. Generally, the mixed anhydride was prepared *via* the common procedure by heating the mixture of several equivalents of cyanoacetic acid and anhydrides [10].

In the first approach, the synthesis of 3-oxopropanenitriles was performed by the addition of cyanoacetic acid–acetic anhydride, without catalyst, using pyrrole, thiophene, and furan derivatives as starting materials. In these conditions, no reaction was observed for thiophene and furan derivatives, and therefore, Scheme 2 represents only the synthetic pathways for the pyrrole based molecules.

Using **1**(**a–e**) as substrates, 3-oxopropanenitriles **2**(**a–e**) were obtained in 30–85% yield, with a cyanoacetylating agent containing 2:3 ratio between cyanoacetic acid and acetic anhydride (Table 1).

The highest yields were obtained for pyrrole, because of its high reactivity; it can be noticed that the introduction of a phenyl group at the nitrogen atom (**1c** and **1d**) or in the alpha position (**1e**) leads to a significant yield decrease, as a direct consequence of the strong steric hindrance.

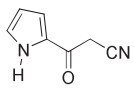
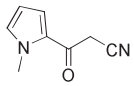
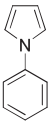
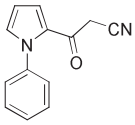
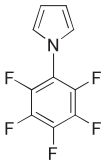
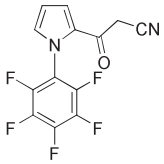
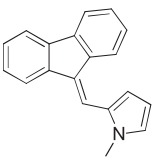
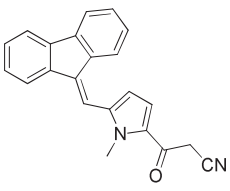
Scheme 2. Synthesis of 3-oxopropanenitriles using cyanoacetic acid: acetic anhydride mixture



R = H, 9-ethylidene-9*H*-fluorene
X = NH, N(CH_3), N-phenyl, N-pentafluorophenyl

Table 1

Substituted 3-oxopropanenitriles **2**(**a-e**) synthesized by cyanoacetic acid: acetic anhydride mixture.

Substrate		Product (2)		Yield
1a		**2a**		85%
1b		**2b**		57%
1c		**2c**		36%
1d		**2d**		30%
1e		**2e**		48%

Except for compounds **1c** and **1d**, where secondary products were isolated 1-(1-phenyl-1*H*-pyrrol-2-yl)ethan-1-one (**3c**) [11] in 5% and 1-(1-(perfluorophenyl)-1*H*-pyrrol-2-yl) ethan-1-one (**3d**) [12] in 24% yields, in the other cases these compounds were not found.

In order to extend the applicability of this reaction to less reactive electron poor aromatic compounds, stronger conditions are necessary. Therefore, in a our second approach, the acetic acid anhydride is replaced with trifluoroacetic anhydride and $Mg(ClO_4)_2{\cdot}2H_2O$ is added as catalyst.

We have already noticed in our previous work that Mg $(ClO_4)_2{\cdot}2H_2O$ acts as a Lewis acid and improves the eaction yield [13].

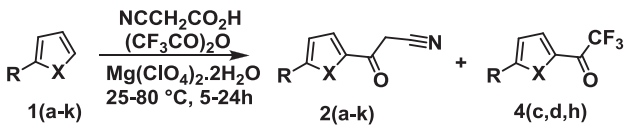
Using mixed anhydride derived from cyanoacetic acid: trifluoroacetic anhydride together with the perchlorate catalyst, 3-oxopropanenitriles of different heteroaromatic compounds were obtained with satisfactory yields (Scheme 3).

Different anhydride:acid ratios were used in order to optimize the reaction yields. If the ratio of the trifluoroacetic anhydride:cyanoacetic acid is 1:2 and the reaction underwent at 25°C for 30 min, trifluoroacetyl derivatives **4**(**c**, **d**, **h**) were isolated as secondary products in 32%, 10%, and respectively 28% yields. In order to eliminate the by-product formation, the reaction conditions were appropriately modified. Therefore, during the preparation of the mixed anhydride at 50°C for 30 min, the generated trifluoroacetic acid was removed via vacuum distillation during the reaction, monitored by TLC, and the formation of by-product **4** was avoided. The complete conversion of the starting materials **1**(**a–k**) was not achieved in any presented compounds. The best results obtained for different heterocyclic compounds are summarized in Table 2. Several interesting features are coming out from the results shown in Table 1 and Table 2.

Regarding the pyrrole derivatives with bulky phenyl or pentafluorophenyl substituents (**1c** and **1d**), the trifluoroacetic anhydride:cyanoacetic acid is more efficient (61–65% yields) with respect to acetic anhydride: cyanoacetic acid (30–36% yields). The scope and limitations of a direct cyanoacetylation were overcome, because the reaction works well with different active five-membered heterocycles. The reaction conditions were suitable also for the cyanoacetylation of the unsubstituted thiophene **1f** and furan **1j**, in 39% and respectively, 23%.

Obviously the reaction of activated derivatives **1**(**g–i**, **k**) proceeded in a higher yields (43–49%).

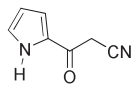
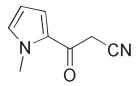
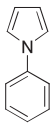
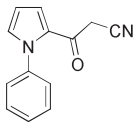
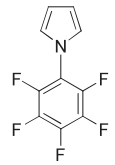
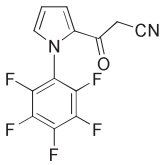
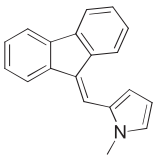
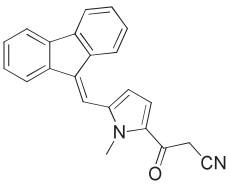
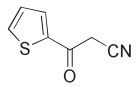
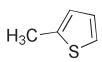
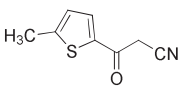
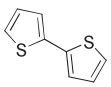
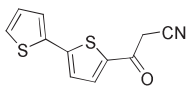
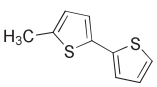
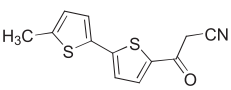
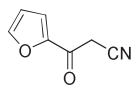
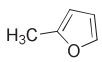
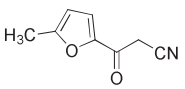
Scheme 3. Synthesis of 3-oxopropanenitriles **2**(**a–k**) by cyanoacetic acid:trifluoroacetic anhydride mixture, in the presence of 0.01 eqv. of $Mg(ClO_4)_2{\cdot}2H_2O$.



R = H, thiophene, 2-methylthiophene, 9-ethylidene-9*H*-fluorene
X = S, NH, N(CH_3), N-phenyl, N-pentafluorophenyl

Table 2

Substituted 3-oxopropanenitriles **2**(**a–k**) synthesized by mixed anhydride–cyanoacetic acid:trifluoroacetic anhydride.

Substrate		Product (2)		Yield
1a		**2a**		31%[a]
1b		**2b**		85%[a]
1c		**2c**		61%[a]
1d		**2d**		65%[a]
1e		**2e**		65%[a]
1f		**2f**		39%[b]
1g		**2g**		48%[a]
1h		**2h**		29%[b]
1i		**2i**		49%[b]
1j		**2j**		23%[a]
1k		**2k**		43%[a]

[a]Isolated yield using cyanoacetic acid:trifluoroacetic anhydride 1:2, $Mg(ClO_4)_2{\cdot}2H_2O$ (0.01 equiv.).
[b]Isolated yield using cyanoacetic acid:trifluoroacetic anhydride 1:2, $Mg(ClO_4)_2{\cdot}2H_2O$ (0.01 equiv.), removing the trifluoroacetic acid from the reaction media.

The structures of all synthesized compounds were established on the basis of their spectroscopic data. The IR spectrum of compounds **2**(**a–k**) showed a strong absorption at 2210–2259 cm^{-1} because of the CN group. The ^1H NMR spectrum of **2**(**a–k**) showed a singlet at 3.8–3.9 ppm corresponding to CH_2 groups. The carbon signals of the target 3-oxopropanenitrile group are appeared with shift around 29 (CH_2), 113 (CN), and 175 (CO) ppm. ^{19}F NMR spectra displayed two triplets and one doublet in a 2:1:2 ratios which characterize the pentafluorophenyl group of **2d** and **4d** derivatives and one singlet from CF_3 which characterize the trifluoroacetic group of byproducts **4c**, **4d**, and **4h**.

CONCLUSIONS

In summary, we have described an efficient method which allows a facile and direct synthesis of heteroaryl 3-oxopropanenitriles. These synthetic procedures are valuable because mixed anhydrides are employed and almost in all cases commercially available starting materials were used. These synthetic pathways represent new methods for the direct preparation of 3-oxopropanenitriles of thiophene and furan derivatives, which are less reactive comparing to the substituted pyrroles. Moreover, the target compounds **2**(**a–k**) may be used as intermediates to develop novel heterocyclic compounds with potential biological activity.

EXPERIMENTAL

General. All starting materials and substrates are commercially available (Sigma-Aldrich), except 1-phenyl-1*H*-pyrrole (**1c**) [14] which was synthesized from aniline hydrochloride and 2,5-dimethoxytetrahydrofuran, 1-pentafluorophenyl-1*H*-pyrrole (**1d**) [12] prepared by a modified Clauson–Kass cyclization and 2-((9*H*-fluorenylidene)methyl)-1-methyl-1*H*-pyrrole (**1e**) [2] was obtained as a condensation product from the reaction of 1-methyl-1*H*-pyrrole-2-carbaldehyde and fluorene. Compounds **1c**, **1d**, and **1e** were purchased from Georganics. Melting points were recorded on a Kofler block and are uncorrected. Infrared spectra (KBr) were determined on a Perkin-Elmer 1600 FT-IR system. NMR spectra (^1H at 300, ^{13}C at 75, and ^{19}F at 300 MHz) were obtained in deuterochloroform using VARIAN VXR 300 spectrometer with tetramethylsilane as internal standard. Chemical shifts are reported in parts per million (ppm). Coupling constants are reported in Hertz (Hz). Elemental analyses were measured with Carlo Erba Elemental Analyzer 1108. Silica gel 60 (230–400 mesh, Merck) was used for column chromatography. Reactions and the collected fraction samples were monitored by TLC (Merck 60 F254 silica gel). The ^1H NMR spectra of the isolated acetyl by-products 3 were in concordance with that reported in the literature.

General procedures for the synthesis of heterocyclic 3-oxopropanenitrile. Cyanoacetic acid–acetic anhydride method. The mixed anhydride was prepared from cyanoacetic acid and acetic anhydride (in 3:2 ratio) the appropriate heterocyclic derivative (**1a–j**, 1.0 equiv.) was added at 80°C under argon atmosphere and stirred at this temperature for a further 4 h. The reaction mixture was then poured into ice water, and then saturated solution of $NaHCO_3$ was added (pH = 7). The product was extracted by CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and the solvent removed in vacuo to dryness to give the crude product.

Cyanoacetic acid–trifluoroacetic anhydride method. The mixed anhydride was prepared from cyanoacetic acid and trifluoroacetic anhydride (in 2:1 ratio); the appropriate heterocyclic derivative (**1a–k**) and catalytic amount of $Mg(ClO_4)_2 \cdot 2H_2O$ (0.01 equiv.) were added at 25°C under argon atmosphere and stirred at this temperature for 4–20 h. The reaction mixture was then poured into water, and then saturated solution of $NaHCO_3$ was added (pH = 7). The product was extracted by CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and the solvent was removed in *vacuo* to dryness to give the crude product.

3-Oxo-3-(1H-pyrrole-2-yl)propanenitrile (2a). Crystallized from ethanol, colorless solid, mp 78–81°C (Lit. [7] mp 78°C).

3-Oxo-3-(1-methyl-1H-pyrrole-2-yl)propanenitrile (2b). Crystallized from ethanol, colorless solid, mp 109–110°C (Lit. [7] mp 109–110°C).

3-Oxo-3-(1-phenyl-1H-pyrrole-2-yl)propanenitrile (2c). Purified by column chromatography (hexane:ethyl acetate, 5:1) and recrystallized from methanol, colorless solid, mp 95°C.

IR (KBr) υ: 720, 900, 1050, 1105, 1270, 1325, 1380, 1490, 1679, 1684, 2210, 3490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (2H, s, CH2), 6.37–6.35 (1H, dd, J = 2.8 Hz, 3.4 Hz), 7.12–7.05 (2H, m), 7.27–7.24 (2H, m), 7.43–7.41 (3H, m); ^{13}C NMR (CDCl3) δ: 29.5, 110.4, 114.2, 121.3, 126.5, 128.3, 128.5, 129.1, 133.6, 139.9, 175.3. *Anal.* Calcd. for $C_{13}H_{10}N_2O$: 74.27; H, 4.79; N, 13.33. Found: C, 74.32; H, 4.81; N, 13.35.

3-Oxo-3-(1-(perfluorophenyl)-1H-pyrrole-2-yl)propanenitrile (2d). Purified by column chromatography (hexane:ethyl acetate, 5:1) and recrystallized from methanol, colorless solid, mp 105–106°C. IR (KBr) υ: 750, 810, 990, 1050, 1100, 1175, 1405, 1510, 1530, 1675, 2220, 3430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (2H, s, CH2), 6.52 (1H, dd, J = 2.7 Hz, 3.4 Hz), 7.02 (1H, s), 7.21 (1H, d, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ: 29.1, 112.0, 113.5, 121.8, 129.0, 132.7, 145.4–135.9 (5 × s, C–F), 176.1; ^{19}F NMR ($CDCl_3$) δ: −83.90 (2 F, t, J = 8.7 Hz), −75.17 (1 F, t, J = 11.4 Hz), −69.45 (2 F, d, J = 9.0 Hz). *Anal.* Calcd. for $C_{13}H_5F_5N_2O$: C, 52.01; H, 4.68; N, 9.33. Found: C, 52.32; H, 4.70; N, 9.57.

3-Oxo-3-(5-((9H-fluorene-9-ylidene)methyl)-1-methyl-1H-pyrrole-2-yl)propanenitrile (2e). Yellow solid, mp 133–135°C (Lit. [2i] mp 133–135°C).

3-Oxo-3-(thiophene-2-yl)propanenitrile (2f). Crystallized from ethanol, colorless solid, mp 123–126°C, (Lit. [15] mp 124–126°C; ethanol).

3-Oxo-3-(5-methylthiophene-2-yl)propanenitrile (2g). Crystallized from ethanol, colorless solid, mp 111–112°C (Lit. [16] mp 108–109°C).

3-Oxo-3-(2,2′-bithiophene-5-yl)propanenitrile (2h). Purified by column chromatography (dichloromethane) and recrystallized from ethanol, yellow solid, mp 127–128°C. IR (KBr) υ: 668, 723, 772, 796, 841, 879, 1075, 1227, 1336, 1393, 1455, 1507, 1541, 1558, 1666, 1699, 2259, 2340 cm^{-1}; ^1H NMR (CDCl3) δ 3.97 (2H, s, CH2), 7.08 (1H, dd, J = 4.2 Hz, 4.3 Hz), 7.22 (1H, d, J = 4.2 Hz), 7.39–7.36 (2H, m), 7.67 (1H, d, J = 3.9 Hz,); ^{13}C NMR (CDCl3) δ: 29.1, 113.5, 124.4, 126.5, 127.5, 128.5, 134.6, 135.5, 138.3, 148.5, 178.9. *Anal.* Calcd for $C_{11}H_7NOS_2$: 56.63; H, 3.02; N, 6.00. Found: C, 56.51; H, 3.00; N, 6.01.

3-Oxo-5′-methyl-(2,2´-bithiophene-5-yl)propanenitrile (2i). Purified by column chromatography (dichloromethane) and recrystallized from ethanol, yellow solid, mp 172–174°C. IR (KBr) υ: 668, 798, 897, 1074, 1233, 1330, 1442, 1472, 1521, 1507, 1540, 1684, 1699, 2258, 2340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (3H, s, CH3), 3.95 (2H, s, CH2), 6.73 (1H, d, J = 3.6 Hz), 7.12 (1H, d, J = 4.2 Hz), 7.17 (1H, d, J = 3.6 Hz), 7.64 (1H, d, J = 4.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.5, 29.1, 113.6, 123.6, 126.6, 126.7, 133.2, 134.7, 137.6, 142.9, 149.1, 178.7. *Anal.* Calcd. for C12H9NOS2: 58.27; H, 3.67; N, 5.66. Found: C, 58.30; H, 3.68; N, 5.65.

3-Oxo-3-(furan-2-yl)propanenitrile (2j). Crystallized from ethanol, colorless solid, mp 77–79°C (Lit.4 mp 74–75°C).

3-Oxo-3-(5-methylfuran-2-yl)propanenitrile (2k). Crystallized from ethanol, colorless solid, mp 89–92°C. ^1H NMR ($CDCl_3$) δ 2.43 (3H, s, CH3), 3.92 (2H, s, CH2), 6.27 (1H, d, J = 3.0 Hz), 7.30 (1H, d, J = 3.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 14.1, 28.4, 110.2, 113.6, 121.4, 149.1, 159.6, 174.7. *Anal.* Calcd. for C8H7NO2: C, 64.42; H, 4.73; N, 9.39. Found C, 64.57; H, 4.88; N, 9.41.

2,2,2-Trifluoro-1-(1-phenyl-1H-pyrrole-2-yl)ethanone (4c). Purified by column chromatography (hexane:ethyl acetate, 5:1) and recrystallized from hexane, colorless solid, yield 32% (0.5 g), mp 36–37°C. (Lit. [17]).

2,2,2-Trifluoro-1-(1-(perfluorophenyl)-1H-pyrrole-2-yl)ethanone (4d). Purified by column chromatography (hexane:ethyl acetate, 5:1) and recrystallized from hexane, colorless solid, yield 10% (0.08 g), mp 48–49°C. ^1H NMR ($CDCl_3$) δ 6.62–6.60 (1H, dd, J = 2.6 Hz), 7.15–7.13 (1H, m), 7.49–7.46 (1H, m); ^{13}C NMR ($CDCl_3$) δ: 110.7, 113.1, 116.4 (q, JF-C = 288.3 Hz, $COCF_3$), 125.2, 134.5, 145.5–141.9 (5 × C–F), 169.9 (q, JF-C = 36.5 Hz, $COCF_3$); ^{19}F NMR ($CDCl_3$, HFB) δ −73.1 (3 F, s, $COCF_3$); −147.9 (2 F, t), −153.3 (1 F, t), −162.4 (2 F, d). *Anal.* Calcd. for $C_{12}H_3F_8NO$: C, 43.79; H, 0.92; N, 4.26. Found: C, 44.52; H, 0.94; N, 4.31.

1-(2,2′-Bithiophene-5-yl)-2,2,2-trifluoroethanone (4h). Purified by column chromatography (hexane/ethyl acetate, 9/1), and recrystallized from ethanol, colorless solid, yield 28% (0.44 g), mp 65–67°C. ^1H NMR ($CDCl_3$) δ 7.11 (1H, dd, J = 4.2 Hz, 4.5 Hz), 7.26 (1H, d, J = 4.2 Hz), 7.43–7.41 (2H, m), 7.87–7.85 (1H, m); ^{13}C NMR ($CDCl_3$) δ: 116.4 (q, JF-C = 288.5 Hz, $COCF_3$), 124.9, 127.0, 128.1, 128.6, 133.9, 135.3, 137.5, 150.2, 173.1 (q, JC-F = 36.4 Hz, $COCF_3$); ^{19}F NMR ($CDCl_3$) δ −96.4 (s, 3 F, $COCF_3$). *Anal.* Calcd. for $C_{10}H_5F_3OS_2$: C, 45.79; H, 1.92. Found: C, 46.62; H, 1.90.

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