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tert-Butoxide-Mediated Arylation of 2-Substituted Cyanoacetates with Diaryliodonium Salts

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Abstract: A transition metal-free direct arylation of 2-substituted cyanoacetates with diaryliodonium salts was developed. With this approach, a wide range of α-tolunitrile derivatives has been synthesized in good to excellent yields of 45–92%. Furthermore, the practicability of this approach is further manifested in the synthesis of a related bioactive agent of glutarimide.

Keywords: α-arylacetonitriles; arylation; diaryliodonium salts; metal-free conditions; nitriles

Introduction

Nitriles are valuable synthons that can serve as precursors to amines, carboxylic acids, carboxamides, aldehydes, ketones, and even hetercycles.[1] Furthermore, over 50 nitrile-containing agents are prescribed for either medicinal indications as pharmaceuticals or undergoing clinical development.[2] Particularly, α-arylacetonitriles containing the nitrile group on a quaternary carbon adjacent to an aromatic ring, are structurally interesting in medical research. For example, anastrazole, verapamil, and piritramide are widely prescribed for treating estrogen-dependent breast cancer, angina and postoperative pain, respectively.[3] Cilomilast is one of the well studied nitrile-containing leads as an anti-inflammatory and antiasthmatic agent (Figure 1).[4]

With regard to the preparation of versatile synthons of 2-alkyl-2-arylcyanoacetates, several powerful approaches essentially involving transition metal (such as palladium or copper) catalyzed α-arylation of 2-cyanoacetate esters with aryl halides, are well recorded.[5] But the requirement of heavy metals with special ligands in these arylation reactions limits the practical applications due to the major problems caused by purification and economic cost. Furthermore, functional group tolerance in these catalytic systems with labile metal-phosphine complexes also received much consideration.[5] Notably, the direct coupling reaction between aryl halides and simple 2-alkylcyanoacetates such as ethyl 2-methylcyanoacetate proved to be a practically difficult task with these catalytic systems.[5c]

Recently, our laboratory has reported the metal-free *C*-arylation of tetrahydrocarbazoles, pyrazolin-5-ones and 1-acetylindolin-3-ones.[6] In recent years, other valuable nucleophiles such as ethyl acetoace-

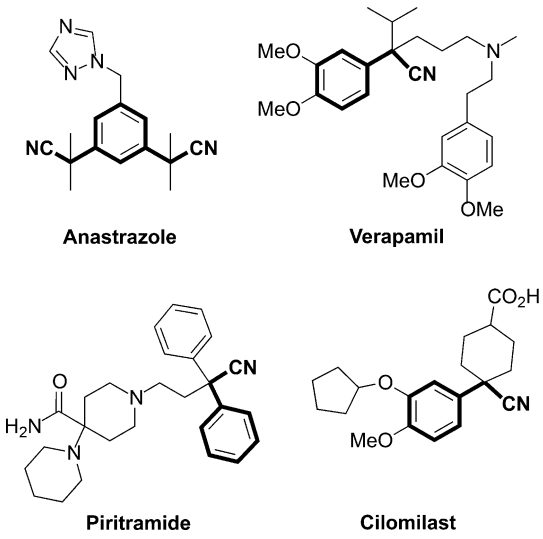


Figure 1. Selected examples of pharmaceutical agents containing α-arylacetonitriles.

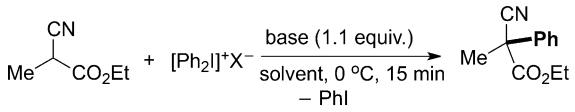
tates, azlactones and nitro compounds were arylated using diaryliodonium salts in a basic reaction environment.[7] Very recently, Gaunt reported two cases of the fluoride counteranion within the diaryliodonium salts triggered *C*-arylation of α-cyano-α-phenyl esters in good yields under metal-free reaction conditions.[8] In the context of our general interest in the synthesis of medically useful compounds by arylation of nucleophiles using iodonium salts, we were intrigued by the possibility of metal-free arylation towards nitrile-containing 2-arylcyanoacetates. Herein we present the potassium *tert*-butoxide-mediated arylation of 2-substiuted cyanoacetates, giving an efficient access to 2-arylcyanoacetates.

Results and Discussion

We began our study using diphenyliodonium triflate (**2a**) and ethyl 2-methylcyanoacetate (**1a**) to optimize the conditions (Table 1). We were pleased to find that the reaction gave the desired product ethyl 2-cyano-2-phenylpropanoate (**3a**) in 70% yield in the presence of potassium *tert*-butoxide as the base and toluene as solvent at 0 °C. As shown in Table 1, after examining several solvents, it is found that the reaction worked well in dichloromethane (CH_2Cl_2), which give **3a** in a high yield of 92% (Table 1, entry 5). Screening various bases revealed that strong base potassium *tert*-butoxide in CH_2Cl_2 delivered the desired product **3a** in the most efficient manner (Table 1, entries 5–9). We also tried the reaction under air conditions, the yield of **3a** was slightly decreased (Table 1, entry 10). Furthermore, we evaluated different anions of the diphenyliodonium salts, a negligible influence was observed on the yield of desired product of **3a** (Table 1, entries 11–13).

With the optimal conditions established, we subsequently examined various diaryliodonium salts as arylation partners. Generally, as shown in Table 2, this reaction system could tolerate a variety of functional groups on the diphenyliodonium salts, and the reactions were completed in the short time of fifteen minutes as determined by thin-layer chromatography. For symmetrical diaryliodonium salts, the reaction was significantly affected by the electronic nature of the aromatic rings (Table 2, entries 1–11). It was observed that diaryliodonium salts bearing electron-donating substituents, such as methoxy, alkyl and halo groups on the phenyl ring, favoured the reaction in terms of isolated yields of desired products. While substrates with electron-withdrawing groups ester or

Table 1. Screening of reaction conditions for the arylation of ethyl 2-methylcyanoacetate.[a]

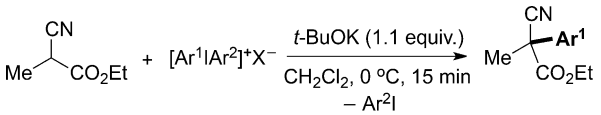


1a 2 3a

Entry	X[b]	Base	Solvent	Yield [%][c]
1	OTf	*t*-BuOK	toluene	70
2[d]	OTf	*t*-BuOK	DCE	46
3	OTf	*t*-BuOK	MeCN	58
4	OTf	*t*-BuOK	THF	33
5	OTf	*t*-BuOK	CH_2Cl_2	92
6	OTf	K_2CO_3	CH_2Cl_2	40
7	OTf	NaOH	CH_2Cl_2	64
8	OTf	NaH	CH_2Cl_2	68
9	OTf	DMAP	CH_2Cl_2	30
10[e]	OTf	*t*-BuOK	CH_2Cl_2	75
11	OTs	*t*-BuOK	CH_2Cl_2	84
12	BF_4	*t*-BuOK	CH_2Cl_2	90
13	PF_6	*t*-BuOK	CH_2Cl_2	91

[a] Unless otherwise specified, *reaction conditions:* **1a** (0.5 mmol), **2** (0.55 mmol, 1.1 equiv.), base (0.55 mmol, 1.1 equiv.) and solvent (2 mL); 0 °C; 15 min; under nitrogen.
[b] OTf = trifluoromethansulfonate; OTs = 4-toluenesulfonate.
[c] Isolated yield.
[d] DCE = 1,2-dichloroethane.
[e] Under air.

Table 2. Scope of iodonium salts in the arylation of ethyl 2-methylcyanoacetate.[a]



1a 2 3

Entry	$Ar^1(Ar^2)$	X[b]	Product	Yield [%][c]
1	$(4\text{-}t\text{-}BuC_6H_4)_2$	OTf	**3b**	73
2	$(4\text{-}MeC_6H_4)_2$	OTf	**3c**	86
3	$(4\text{-}MeOC_6H_4)_2$	OTf	**3d**	90
4	$(4\text{-}FC_6H_4)_2$	OTf	**3e**	65
5	$(4\text{-}ClC_6H_4)_2$	OTf	**3f**	85
6	$(4\text{-}BrC_6H_4)_2$	OTf	**3g**	77
7	$(3\text{-}CO_2EtC_6H_4)_2$	PF_6	**3h**	34
8	$(3\text{-}NO_2C_6H_4)_2$	PF_6	**3i**	43
9	$(4\text{-}CF_3C_6H_4)_2$	BF_4	**3j**	83
10	$(3,4\text{-}Cl_2C_6H_3)_2$	BF_4	**3k**	68
11	$(2,4\text{-}Me_2C_6H_3)_2$	PF_6	**3l**	72
12	Ph (mesityl)	OTf	**3a**	68
13	$4\text{-}CO_2EtC_6H_4$ (mesityl)	OTf	**3m**	51
14	$3\text{-}CO_2EtC_6H_4$ (mesityl)	OTf	**3h**	32
15	$4\text{-}BrC_6H_4$ (mesityl)	OTf	**3g**	64

[a] Unless otherwise specified, *reaction conditions:* **1a** (0.5 mmol), diaryliodonium salt (0.55 mmol, 1.1 equiv.), base (0.55 mmol, 1.1 equiv.) and solvent (2 mL); 0 °C; 15 min; under nitrogen.
[b] OTf = trifluoromethansulfonate; OTs = 4-toluenesulfonate.
[c] Isolated yield.

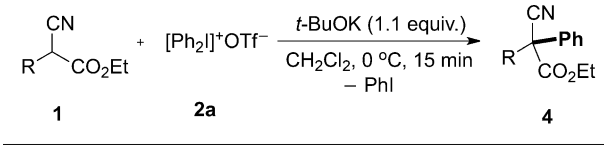
nitro groups on the *meta*-position of benzene ring, gave relatively low yields of 34% and 43%, respectively (Table 2, entries 7 and 8). For the unsymmetrical diaryliodonium salts, [Ar-I-mesityl]OTf, to test the steric effect on the reactivity, as expected,[9] the less sterically demmanding aromatic group Ar was transferred preferably to the desired products of **3**. No mesitylated product **3** was observed (Table 2, entries 12–15). In comparison with the iodonium salt [4-$CO_2EtC_6H_4$-I-Mesityl]OTf bearing an ester group on the *para*-position, the ester groups on the *meta*-position of diaryliodonium salt gave a relative low yield (32% yield of **3h** *vs.* 51% yield of **3m**; Table 2, entries 13 and 14).

To further investigate the scope of this reaction, a variety of ethyl cyanacetate derivatives were phenylated in the presence of potassium *tert*-butoxide at the temperature of 0 °C. These conditions proved to be efficient in the phenylation as shown in Table 3. Generally, 2-phenyl-2-alkylcyanoacetates **4** were obtained in excellent yields of 77–92% when the R of **1** is alkyl (Table 3, entries 1–7). Among them, when R is fluoroalkyl or allyl, **4e** and **4f** can be furnished in good yields of 81% and 77%, respectiviely. Moreover, when **1** bearing benzyl and aromatic rings were employed, the phenylated products **4h**–**4n** were readily prepared in the good yields of 65–82% (Table 3, entries 8–14). When R of **1** is phenacyl, the phenylation product **4o** was provided in a moderate yield of 45% (Table 3, entry 15).

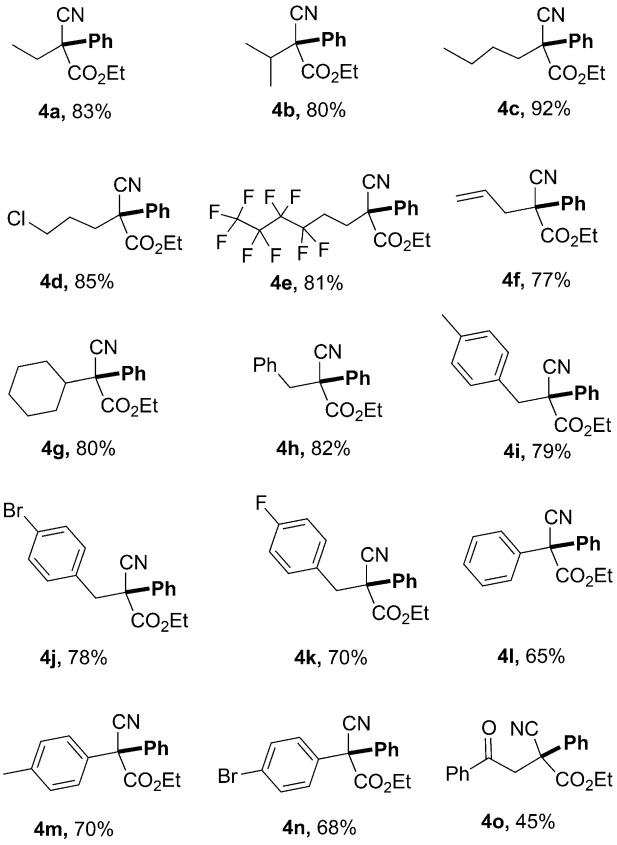
Although it is difficult to draw a precise mechanism at this stage, according to the previous reports, the metal-free arylation using diaryliodonium salts can proceed either through an SET mechanism[10a] or *via* a ligand exchange pathway.[10b,c] Therefore, as shown in Scheme 1, deprotonation of **1a** by *t*-BuOK generated **5** and/or the corresponding enolate **6** in the basic environment. Two pathways *via* different intermediates **7** or **8** by electronic attack with diaryliodonium salts could give the final product **3a** along with an aryl iodide, respectively.

Finally, utilization of the arylation for conversion of the products into useful molecules was attempted (Scheme 2). Glutarimides were reported to possess neuroplegic, immunomodulatory and anticancer activity.[11] According to the reported synthetic route,[12] 2-phenylbutanenitrile is an important intermediate to prepare glutethimide. The direct arylation of alkyl nitriles had been attempted firstly, while it led to the decomposition of the diaryliodonium salts, no arylation product was observed. Hence, the arylation of methyl 2-cyanobutanoate **9** was conducted under the standard conditions. The desired product **10** was obtained in the yield of 84%. The decarboxylation of **10** delivered the key intermediate **11** in 92% yield. The further synthetic procedure involving Michael addition with acrylic ester, two steps of hydrolysis and cyc-

Table 3. Arylation of 2-substituted cyanoacetates **1**.[a,b]

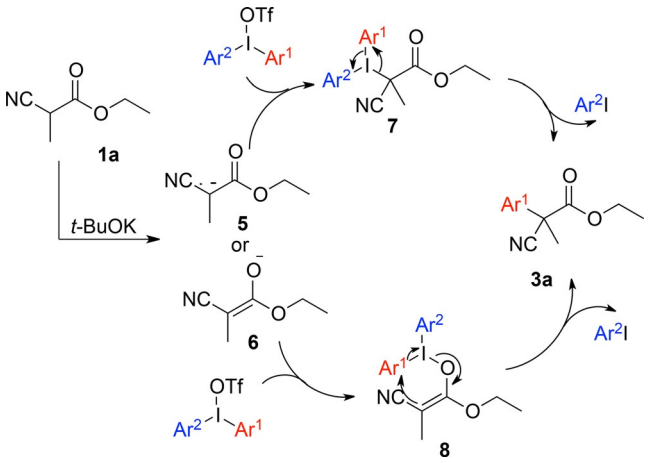


1 2a 4

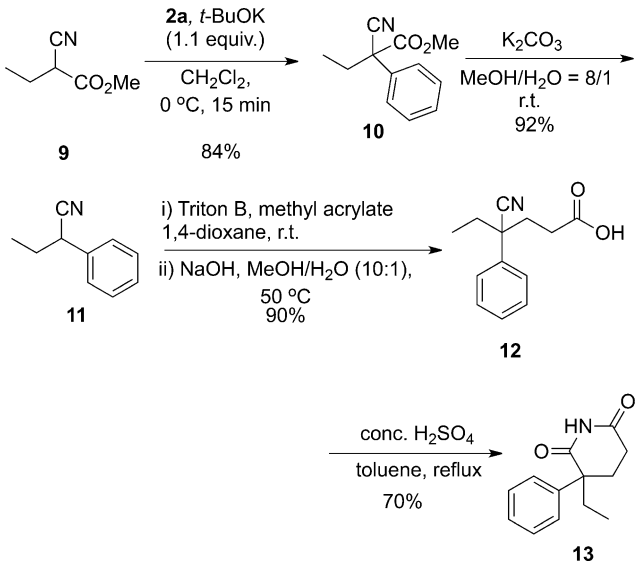


[a] Unless otherwise specified, *reaction conditions:* **1** (0.5 mmol), diphenyliodonium salt (0.55 mmol, 1.1 equiv.), base (0.55 mmol, 1.1 equiv.) and solvent (2 mL); 0 °C; 15 min; under nitrogen.

[b] Isolated yield.



Scheme 1. Proposed mechanism.



Scheme 2. Synthesis of glutethimide.

lization gave the final product of **13** for which the analytical data corresponded to those in the literature.[12,13]

Conclusions

In summary, we have demonstrated a direct arylation of ethyl 2-cyanobutanoate derivatives by using diaryliodonium salts under transition metal-free conditions. The synthetic method was extended to substrates bearing a variety of functional groups. As such, various 2-substituted α-arylacetonitriles were prepared in good yields, which are valuable chemical intermediates in medical research. Furthermore, glutethimide was prepared by using this approach as the key step, which demonstrates the potential applications of this method in organic synthesis.

Experimental Section

General Methods

All reagents were obtained from commercial sources without further purification and the solvents were purified by standard techniques. The diaryliodonium salts were prepared according to the literature report.[14] All reactions were performed in oven-dried glassware containing a Teflon-coated stirrer bar and dry septum under a nitrogen atmosphere. ^{1}H NMR and ^{13}C NMR spectra were respectively recorded at 400 and 100 MHz, using tetramethylsilane as an internal reference. Chemical shifts (δ) and coupling constants (J) were expressed in parts per million and hertz, respectively. High-resolution mass spectrometry (HR-MS) was performed on an EI-TOF spectrometer. Mass spectra were recorded by the mass spectrometry service of Shanghai Institute of Organic Chemistry. Column chromatography was performed on silica gel (Huang-hai, 300–400 mesh).

Typical Procedure for Arylation of 2-Substiuted Cyanoacetates

An oven-dried Schlenk tube was charged with 2-substituted cyanoacetate (0.5 mmol, 1 equiv.), the tube was evacuated and backfilled with nitrogen, then 2 mL anhydrous CH_2Cl_2 and potassium *tert*-butoxide (61.7 mg, 0.55 mmol, 1.1 equiv.) were added, the mixture was stirred at 0 °C for 5 min. The solution of diaryliodonium salt (0.55 mmol, 1.1 equiv.) in 2 mL anhydrous CH_2Cl_2 was added through a syringe subsequently for 5 min. the reaction was stirred for another 15 min. The reaction mixture was quenched with 20 mL water, and then extracted with ethyl acetate (30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and filtered. After the solvent was removed under vacuum, the residue was purified by flash chromatography to give the desired product.

Ethyl 2-cyano-2-phenylpropanoate (3a):[5c] Colorless oil; yield: 93.5 mg (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.52 (m, 2H), 7.43–7.35 (m, 3H), 4.30–4.17 (m, 2H), 1.95 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.9, 135.8, 129.2 128.8, 125.7, 119.6, 63.3, 48.3, 24.9, 13.8.

Ethyl 2-(4-*tert*-butylphenyl)-2-cyanopropanoate (3b): Colorless oil; yield: 94.6 mg (73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.40 (m, 4H), 4.29–4.19 (m, 2H), 1.94 (s, 3H), 1.32 (s, 9H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1, 151.9, 132.8, 126.1, 125.5, 119.7, 63.2, 47.9, 34.6, 31.2, 24.9, 13.8; HR-MS (EI): m/z = 259.1574, calcd. for $C_{16}H_{21}NO_2$ $[M]^+$: 259.1572.

Ethyl 2-cyano-2-*p*-tolylpropanoate (3c):[15a] Colorless oil; yield: 93.4 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 2H), 7.21 (d, J = 8.2 Hz, 2H), 4.27–4.18 (m, 2H), 2.36 (s, 3H), 1.93 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1, 138.8, 132.9, 129.8, 125.6, 119.7, 63.2, 47.9, 24.8, 21.0, 13.8.

Ethyl 2-cyano-2-(4-methoxyphenyl)propanoate (3d):[15a] Colorless oil; yield: 105.0 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47–7.43 (m, 2H), 6.94–6.90 (m, 2H), 4.27–4.19 (m, 2H), 3.81 (s, 3H), 1.93 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.2, 159.9, 127.7, 127.0, 119.81, 114.4, 63.2, 55.4, 47.6, 24.8, 13.8.

Ethyl 2-cyano-2-(4-fluorophenyl)propanoate (3e):[15a] Colorless oil; yield: 71.9 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.51 (m, 2H), 7.13–7.08 (m, 2H), 4.29–4.20 (m, 2H), 1.95 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.8, 162.8 (d, J = 247.3 Hz), 131.6 (d, J = 3.4 Hz), 127.8 (d, J = 8.4 Hz), 119.4, 116.1 (d, J = 22.0 Hz), 63.4, 47.7, 24.8, 13.8.

Ethyl 2-(4-chlorophenyl)-2-cyanopropanoate (3f):[5c] Colorless oil; yield: 101.0 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.48 (m, 2H), 7.40–7.38 (m, 2H), 4.31–4.18 (m, 2H), 1.94 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.6, 135.0, 134.3, 129.3, 127.3, 119.2, 63.5, 47.8, 24.8, 13.8.

Ethyl 2-(4-bromophenyl)-2-cyanopropanoate (3g): Colorless oil; yield: 108.6 mg (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.53 (m, 2H), 7.43–7.40 (m, 2H), 4.31–4.18 (m, 2H), 1.94 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR

(101 MHz, $CDCl_3$): δ = 167.6, 134.8, 132.3, 127.6, 123.2, 119.1, 63.5, 47.9, 24.8, 13.8; HR-MS (EI): *m/z* = 281.0056, calcd. for $C_{12}H_{12}BrNO_2$ $[M]^+$: 281.0051.

Ethyl 3-(2-cyano-1-ethoxy-1-oxopropan-2-yl) benzoate (3h): Colorless oil; yield: 46.8 mg (34%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (t, *J* = 1.8 Hz, 1H), 8.08 (ddd, *J* = 7.8, 5.0, 1.6 Hz, 1H), 7.75 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.52 (dd, *J* = 9.8, 5.8 Hz, 1H), 4.43–4.38 (m, 2H), 4.30–4.22 (m, 2H), 2.00 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.6, 165.7, 136.3, 131.6, 130.3, 130.0, 129.3, 126.8, 119.2, 63.5, 61.4, 48.1, 24.7, 14.3, 13.8; HR-MS (EI): *m/z* = 275.1159, calcd. for $C_{15}H_{17}NO_4$ $[M]^+$: 275.1158.

Ethyl 2-cyano-2-(3-nitrophenyl)propanoate (3i): Colorless oil; yield: 53.4 mg (43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (t, *J* = 2.0 Hz, 1H), 8.27 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 7.94 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.66 (t, *J* = 8.2 Hz, 1H), 4.36–4.23 (m, 2H), 2.04 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.0, 148.6, 137.8, 132.2, 130.4, 124.0, 121.2, 118.5, 63.9, 48.0, 24.8, 13.8; HR-MS (EI): *m/z* = 248.0789, calcd. for $C_{12}H_{12}N_2O_4$ $[M]^+$: 248.0797..

Ethyl 2-cyano-2-[4-(trifluoromethyl)phenyl]propanoate (3j): Colorless oil; yield: 112.5 mg (83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (s, 4H), 4.34–4.21 (m, 2H), 2.00 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.3, 139.7, 131.1 (q, *J* = 32.9 Hz), 126.4, 126.1 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 273.3 Hz), 118.8, 63.6, 48.2, 24.8, 13.7; HR-MS (EI): *m/z* = 272.0904, calcd. for $C_{13}H_{12}F_3NO_2$ $[M+H]^+$: 272.0898.

Ethyl 2-cyano-2-(3,4-dichlorophenyl)propanoate (3k): Colorless oil; yield: 92.5 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 2.4 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.39 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.33–4.20 (m, 2H), 1.95 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.2, 135.8, 133.4, 131.1, 128.0, 125.4, 118.7, 63.7, 47.6, 24.7, 13.8; HR-MS (EI): *m/z* = 271.0168, calcd. for $C_{12}H_{11}Cl_2NO_2$ $[M]^+$: 271.0167.

Ethyl 2-cyano-2-(2,4-dimethylphenyl)propanoate (3l): Colorless oil; yield: 83.3 mg (72%).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 6.8 Hz, 1H), 7.07- 7.04 (m, 2H), 4.31–4.24 (m, 2H), 2.36 (s, 3H), 2.31 (s, 3H), 2.03 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.4, 138.8, 136.3, 133.0, 130.6, 127.3, 126.0, 119.6, 63.2, 46.6, 23.9, 20.9, 19.9, 13.9; HR-MS (EI): *m/z* = 231.1260, calcd. for $C_{14}H_{17}NO_2$ $[M]^+$: 231.1259..

Ethyl 4-(2-cyano-1-ethoxy-1-oxopropan-2-yl)benzoate (3m):[15b] Colorless oil; yield: 70.2 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.30–4.22 (m, 2H), 1.99 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.4, 165.7, 140.3, 131.1, 130.3, 125.9, 119.0, 63.5, 61.3, 48.4, 24.8, 14.3, 13.8.

Ethyl 2-cyano-2-phenylbutanoate (4a):[5c] Colorless oil; yield: 90.2 mg (83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.53 (m, 2H), 7.43–7.34 (m, 3H), 4.30–4.17 (m, 2H), 2.43 (dq, *J* = 14.6, 7.4 Hz, 1H), 2.17 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.6, 134.5, 129.1, 128.8, 126.1, 118.3, 63.1, 55.1, 31.6, 13.8, 9.8.

Ethyl 2-cyano-3-methyl-2-phenylbutanoate (4b): Colorless oil; yield: 92.5 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.61 (m, 2H), 7.42–7.36 (m, 3H), 4.30–4.13 (m, 2H), 2.81 (dt, *J* = 13.4, 6.8 Hz, 1H), 1.26–1.22 (m, 6H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.8, 133.9, 129.0, 128.8, 126.5, 116.8, 63.0, 61.1, 36.1, 19.4, 17.3, 13.9; HR-MS (EI): *m/z* = 231.1260, calcd. for $C_{14}H_{17}NO_2$ $[M]^+$: 231.1259.

Ethyl 2-cyano-2-phenylhexanoate (4c): Colorless oil; yield: 112.8 mg (92%).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.53 (m, 2H), 7.43–7.34 (m, 3H), 4.30–4.16 (m, 2H), 2.41–2.22 (m, 1H), 2.15–2.07(m, 1H), 1.42–1.35 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.7, 134.8, 129.1, 128.8, 125.7, 118.5, 63.1, 54.2, 37.9, 27.6, 22.4, 13.8 (d, *J* = 8.7 Hz); HR-MS (EI): *m/z* = 245.1415, calcd. for $C_{15}H_{19}NO_2$ $[M]^+$: 245.1416.

Ethyl 5-chloro-2-cyano-2-phenylpentanoate (4d): Colorless oil; yield: 112.9 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.50 (m, 2H), 7.48–7.33 (m, 3H), 4.37–4.12 (m, 2H), 3.56 (t, *J* = 6.4 Hz, 2H), 2.52 (ddd, *J* = 13.8, 11.8, 4.6 Hz, 1H), 2.33 (ddd, *J* = 13.8, 12, 4.6 Hz, 1H), 2.02–1.79 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.3, 134.1, 129.3, 129.1, 126.0, 118.1, 63.4, 53.6, 44.0, 35.5, 28.4, 13.8; HR-MS (EI): *m/z* = 265.0872, calcd. for $C_{14}H_{16}ClNO_2$ $[M]^+$: 265.0870.

Ethyl 2-cyano-5,5,6,6,7,7,8,8,8-nonafluoro-2-phenyloctanoate (4e): Colorless oil; yield: 176.3 mg (81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.53 (m, 2H), 7.48–7.40 (m, 3H), 4.33–4.20 (m, 2H), 2.68 (td, *J* = 13.2, 4.2 Hz, 1H), 2.47 (td, *J* = 13.2, 4.2 Hz, 1H), 2.31–2.21 (m, 1H), 2.20–2.05 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 133.3, 129.5 (d, *J* = 10.2 Hz), 125.8, 120.2 (t, *J* = 32.2 Hz), 118.7 (t, *J* = 33.5 Hz), 117.9–117.3 (m), 115.9 (t, *J* = 33.1 Hz), 112.9–107.7 (m), 63.7, 52.9, 29.1, 27.4 (t, *J* = 22.4 Hz), 13.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.31 (d, *J* = 8.8 Hz, 3F), −114.35 to −114.43 (m, 2F), −124.27 (d, *J* = 4.6 Hz, 2F), −126.22 to −126.30 (m, 2F); HR-MS (EI): *m/z* = 435.0882, calcd. for $C_{17}H_{14}F_9NO_2$ $[M]^+$: 435.0881.

Ethyl 2-cyano-2-phenylpent-4-enoate (4f):[5c] Colorless oil; yield: 88.3 mg (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.53 (m, 2H), 7.43–7.35 (m, 3H), 5.80–7.70 (m, 1H), 5.29–5.21 (m, 2H), 4.30–4.17 (m, 2H), 3.12 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.85 (dd, *J* = 14.0, 7.0 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.1, 134.1, 130.7, 129.2, 128.9, 126.2, 121.2, 118.0, 63.2, 54.13, 42.3, 13.9.

Ethyl 2-cyano-2-cyclohexyl-2-phenylacetate (4g): Colorless oil; yield: 108.6 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.2 Hz, 2H), 7.30 (dd, *J* = 16.4, 8.6 Hz, 3H), 4.19–4.05 (m, 2H), 2.35 (t, *J* = 11.0 Hz, 1H), 1.75 (d, *J* = 10.4 Hz, 2H), 1.60 (d, *J* = 8.8 Hz, 2H), 1.41 (d, *J* = 11.8 Hz, 1H), 1.27 (d, *J* = 11.2 Hz, 1H), 1.29–1.00 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.7, 133.4, 129.0, 128.7, 126.6, 117.3, 63.0, 60.5, 45.3, 29.8, 27.2, 26.0 (d, *J* = 8.7 Hz), 25.8, 13.9; HR-MS (EI): *m/z* = 271.1573, calcd. for $C_{17}H_{21}NO_2$ $[M]^+$: 271.1572.

Ethyl 2-cyano-2,3-diphenylpropanoate (4h):[5c] Colorless oil; yield: 114.5 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.53 (m, 2H), 7.39–7.37 (m, 3H), 7.25–7.23 (m, 3H), 7.17–7.14 (m, 2H), 4.25–4.15 (m, 2H), 3.70 (d, *J* = 13.6 Hz, 1H), 3.32 (d, *J* = 13.6 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.4, 134.5, 134.2, 130.5, 129.1, 129.0, 128.4, 127.8, 126.4, 118.0, 63.3, 55.83, 44.2, 13.8.

Ethyl 2-cyano-2-phenyl-3-*p*-tolylpropanoate (4i): Colorless oil; yield: 115.9 mg (79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.38–7.36 (m, 3H), 7.04 (s,

4H), 4.23–4.15 (m, 2H), 3.66 (d, J=13.6 Hz, 1H), 3.27 (d, J=13.6 Hz, 1H), 2.28 (s, 3H), 1.18 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=167.4, 137.4, 134.5, 131.1, 130.3, 129.1, 129.1, 128.9, 126.4, 118.1, 63.3, 56.0, 43.8, 21.2, 13.8; HR-MS (EI): m/z=293.1417, calcd. for $C_{19}H_{19}NO_2$ $[M]^+$: 293.1416.

Ethyl 3-(4-bromophenyl)-2-cyano-2-phenylpropanoate (4j): Colorless oil; 139.7 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.52–7.50 (m, 2H), 7.40–7.35 (m, 5H), 7.01 (d, J=8.4 Hz, 2H), 4.28–4.15 (m, 2H), 3.64 (d, J=13.8 Hz, 1H), 3.27 (d, J=13.8 Hz, 1H), 1.20 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=167.1, 134.1, 133.2, 132.2, 131.5, 129.2, 129.1, 126.3, 122.0, 117.8, 63.5, 55.5, 43.5, 13.8; HR-MS (EI): m/z=357.0366, calcd. for $C_{18}H_{16}BrNO_2$ $[M]^+$: 357.0364.

Ethyl 2-cyano-3-(4-fluorophenyl)-2-phenylpropanoate (4k): Colorless oil; yield: 104.1 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.53–7.51 (m, 2H), 7.41–7.37 (m, 3H), 7.13–7.10 (m, 2H), 6.95–6.90 (m, 2H), 4.28–4.15 (m, 2H), 3.66 (d, J=13.8 Hz, 1H), 3.29 (d, J=13.8 Hz, 1H), 1.19 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=167.2, 162.5 (d, J=247.3 Hz), 134.1, 132.1 (d, J=8.1 Hz), 129.9 (d, J=2.8 Hz), 129.2, 129.1, 126.3, 117.9, 115.2 (d, J=21.4 Hz), 63.4, 55.8 (d, J=1.2 Hz), 43.3, 13.8; HR-MS (EI): m/z=297.1166, calcd. for $C_{18}H_{16}FNO_2$ $[M]^+$: 297.1165..

Ethyl 2-cyano-2,2-diphenylacetate (4l):[15c] Colorless oil; yield: 86.2 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.32–7.29 (m, 10H), 4.26 (q, J=7.2 Hz, 2H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=167.2, 135.9, 129.0, 128.0, 118.8, 63.7, 58.9, 13.9.

Ethyl 2-cyano-2-phenyl-2-*p*-tolylacetate (4m): Colorless oil; yield: 97.8 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.41–7.35 (m, 5H), 7.29–7.27 (m, 2H), 7.19 (d, J=8.2 Hz, 2H), 4.33 (q, J=7.2 Hz, 2H), 2.35 (s, 3H), 1.30 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=167.4, 139.0, 136.1, 132.9, 129.7, 128.9, 128.9, 128.0, 127.9, 118.9, 63.7, 58.6, 21.1, 13.9. HR-MS (EI): m/z=279.1260, calcd. for $C_{18}H_{17}NO_2$ $[M]^+$: 279.1259.

Ethyl 2-(4-bromophenyl)-2-cyano-2-phenylacetate (4n):[8] Colorless oil; yield: 117.0 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.54–7.51 (m, 2H), 7.42–7.37 (m, 5H), 7.30–7.26 (m, 2H), 4.35 (q, J=7.2 Hz, 2H), 1.32 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=166.8, 135.4, 135.0, 132.1, 129.8, 129.2, 129.2, 127.8, 123.4, 118.3, 63.9, 58.3, 13.9.

Ethyl 2-cyano-4-oxo-2,4-diphenylbutanoate (4o): White solid; yield: 69.1 mg (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.80–7.95 (m, 2H), 7.68–7.59 (m, 3H), 7.50–7.42 (m, 5H), 4.38 (dd, J=10.8, 7.2 Hz, 1H), 4.27 (dd, J=10.8, 7.2 Hz, 1H), 4.18 (d, J=18.0 Hz, 1H), 3.76 (d, J=18.0 Hz, 1H), 1.32 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=194.3, 167.3, 135.3, 134.0, 133.6, 129.4, 129.2, 128.83, 128.2, 126.1, 118.5, 63.5, 50.0, 48.4, 13.8; HR-MS (EI): m/z=307.1206, calcd. for $C_{19}H_{17}NO_2$ $[M]^+$: 307.1208.

Procedure for the Synthesis of Glutethimide

Step 1: An oven-dried, 100-mL, three-necked, round-bottom flask was charged with methyl 2-cyanobutanoate (6.35 g, 50 mmol, 1 equiv.), the flask was evacuated and backfilled with nitrogen, then 50 mL anhydrous CH_2Cl_2 and potassium *tert*-butoxide (6.17 g, 55 mmol, 1.1 equiv.) were added. The mixture was stirred at 0 °C for 5 min. The solution of diphenyliodonium salt (21.51 g, 55 mmol, 1.1 equiv.) in 100 mL anhydrous CH_2Cl_2 was added subsequently for about 15 min. After being stirred for another 30 min the reaction mixture was poured into 200 mL H_2O and then extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed under vacuum, the residue was purified by flash chromatography to give **10**; yield: 8.53 g (84%).

Step 2: The product **10** (8.53 g) was dissolved in 80 mL MeOH, 6.91 g K_2CO_3 were dissolved in 20 mL H_2O and poured into the reaction solution. The contents were stirred for 1 h until TLC analysis indicated complete formation of **11**. MeOH was removed under vacuum and the mixture was poured into 100 mL H_2O and then extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and filtered, then the solvent removed to give **11**; yield: 5.56 g (92%).

Step 3: The compound **11** (5.56 g) was dissolved in 50 mL 1,4-dioxane under 0 °C, 3.63 g methyl acrylate and 7.05 g benzyltrimethylammonium hydroxide (Triton B, 50% solution in MeOH) were added subsequently, followed by a further 3 h stirring to complete the reaction. 1,4-Dioxane was removed under vacuum and the reactor contents were cooled to 0 °C, a solution of NaOH (3.06 g, 2 equiv.) in water/MeOH (5 mL/50 mL) was added, and the mixture heated to 50 °C and maintained at this temperature for 3 h to hydrolyze the intermediate. MeOH was removed under vacuum and water was added to maintain the volume. The solution was washed with CH_2Cl_2 (30 mL×3) to remove any non-acidic organic impurities. The aqueous basic layer was acidified to pH 1–2 with 25% w/w H_2SO_4 to precipitate the product **12**; yield: 7.55 g (90%).

Step 4: The product **12** (7.55 g) was dissolved in 50 mL toluene and concentrated H_2SO_4 (0.68 g, 0.2 equiv.) was added, the mixture was heated to reflux for 4 h. After that, the reaction was poured into 200 g ice, then extracted with ethyl acetate, the solvent removed and the residue crystallized in ether to give glutethimide **13**; yield: 5.28 g (70%).

Methyl 2-cyano-2-phenylbutanoate (10):[15d] Colorless oil; yield: 8.53 g (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.47–7.44 (m, 2H), 7.34–7.27 (m, 3H), 3.68 (d, J=0.8 Hz, 3H), 2.35 (dq, J=14.8, 7.4 Hz, 1H), 2.09 (dq, J=14.8, 7.4 Hz, 1H), 0.97 (t, J=7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=167.1, 133.3, 128.1, 127.8, 125.1, 117.2, 53.9, 52.8, 30.6, 8.8.

2-Phenylbutanenitrile (11):[15e] Colorless oil; yield: 5.60 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.39–7.29 (m, 5H), 3.73 (t, J=7.2 Hz, 1H), 1.96–1.89 (m, 2H), 1.06 (t, J=7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=135.8, 129.0, 128.0, 127.3, 120.8, 38.9, 29.2, 11.5.

4-Cyano-4-phenylhexanoic acid (12): White solid; yield: 7.55 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.58 (b, 1H), 7.42–7.32 (m, 5H), 2.57–2.49 (m, 1H), 2.39–2.31 (m, 1H), 2.19–1.94 (m, 4H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=178.3, 136.9, 129.2, 128.1, 126.0, 121.5, 48.3, 35.1, 34.3, 30.2, 9.7; HR-MS (EI): m/z=217.1106, calcd. for $C_{13}H_{15}NO_2$ $[M]^+$: 217.1103.

3-Ethyl-3-phenylpiperidine-2,6-dione (13):[15f] White solid; yield: 5.28 g (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.64 (s, 1H), 7.38–7.34 (m, 2H), 7.28 (d, J=7.8 Hz, 3H), 2.63–2.58 (m, 1H), 2.45–2.36 (m, 2H), 2.27–2.20 (m, 1H), 2.11–2.02 (m, 1H), 1.98–1.88 (m, 1H), 0.87 (t, J=7.4 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 175.4$, 172.8, 138.9, 129.0, 127.6, 126.2, 51.1, 32.9, 29.3, 27.1, 9.1.

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