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Benzotriazole-mediated alkoxyalkylation and acyloxyalkylation

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Abstract—Reactions of readily available and stable 1-(α-alkoxyalkyl)benzotriazoles type **9a**,**b** and **10a**–**d** with a variety of silyl enol ethers **11** or 1,3-dicarbonyl compounds **13** give the expected ketones **12a**–**l** (60–92%), β-keto esters **14a**,**b** (62–67%), and malonates **14c**,**d** (79–88%) in which a tetrahydrofuran or tetrahydropyran moiety has been introduced at the α position. 1-(Benzotriazol-1-yl)alkyl esters **7** are converted by cyanide anion into cyanohydrin esters **15a**–**i** (55–98%).

1. Introduction

N-Substituted benzotriazoles of type Bt–C–X, where X is halogen,[1] nitrogen,[2] sulfur,[3] and oxygen[4] can ionize either (i) by Bt–C bond scission to form alkyleneonium cations C═X$^+$ and Bt$^-$ or (ii) by C–X bond scission to give X$^-$ anion and a benzotriazole stabilized carbocation Bt–C$^+$. Reports from our laboratory have described the use of Bt–C–X (X═O) as precursors for the synthesis of complex organic compounds including classes difficult to prepare.[5] For example, replacement of the benzotriazole moiety in simple 1-(1-alkoxyalkyl)benzotriazoles **1**, or the products of their addition to enol ethers **3**, gives a wide range of α-substituted ethers **2** or 1,3-diethers **4** and **5** (Scheme 1).[6] Compounds of the type of **1** undergo deprotonation followed by quenching with electrophiles and the products undergo acid-catalyzed hydrolysis of the benzotriazole and the alkoxy group to provide ketones **6** (Scheme 1).[7] The Bt–C–OCO compounds **7**[5] are intermediates for the synthesis of carboxylic esters **8**[8] by substitution of benzotriazolyl moiety with an alkyl, alkenyl or aryl group from the corresponding organozinc reagents (Scheme 2).

We have now found that Lewis acid-catalyzed alkoxyalkylations by **9a**,**b** or **10a**–**d** of silyl enol ethers **11**, and 1,3-dicarbonyl compounds **13** provide convenient access to α-substituted ketones **12a**–**l**, β-keto esters **14a**,**b**, and malonates **14c**,**d**. We now also disclose the acyloxyalkylations of cyanide anion by **7** to provide cyanohydrin esters **15**.

2. Results

2.1. Synthesis of β-alkoxy ketones 12

β-Alkoxy ketone units frequently occur in antibiotics[9] and steroidal frameworks[10] and are precursors for β-hydroxy ketone and *syn*-1,3-diol units, common structural features imbedded in numerous natural products, e.g., rutamycin B and oligomycin C,[11] erythromycins,[12] amphotericin B,[13] and rofllamycoin.[14] β-Alkoxy ketones are typically prepared by: (i) oxidative C–C bond formation reactions of electron-rich alkylbenzyl ethers with trimethylvinyloxysilane (derived from PhCOCH$_3$) catalyzed by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ);[15] (ii) direct alcohol addition to enones;[16] and (iii) Mukaiyama aldol-type condensation of silyl enol ethers. Method iii has been a subject of extensive investigations in which silyl enol ethers undergo a Lewis acid-catalyzed coupling to an acetal (Scheme 3).[17]

We have previously demonstrated that 1-α-benzotriazolylalkyl alkyl ethers **1** behave analogously to acetals, but because the benzotriazolyl substituent is a better leaving group, compounds of type **1** are frequently effective for alkoxyalkylation of ketones and Grignard reagents where the corresponding acetals fail.[6a,18] We now find that the use of benzotriazole adducts (type **9a**,**b** and **10a**–**d**) in the place

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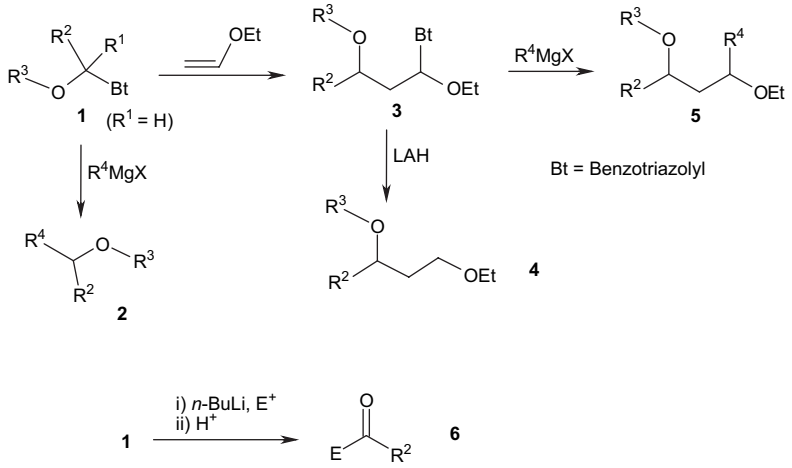
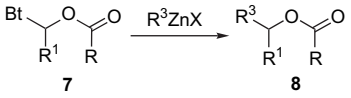
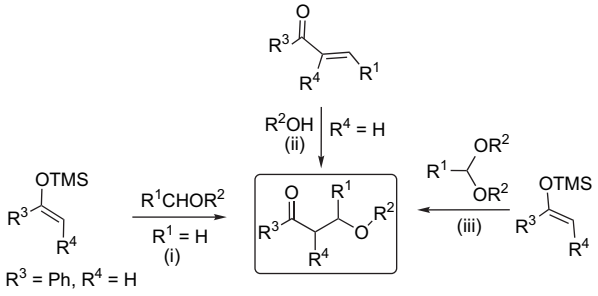


Scheme 1.

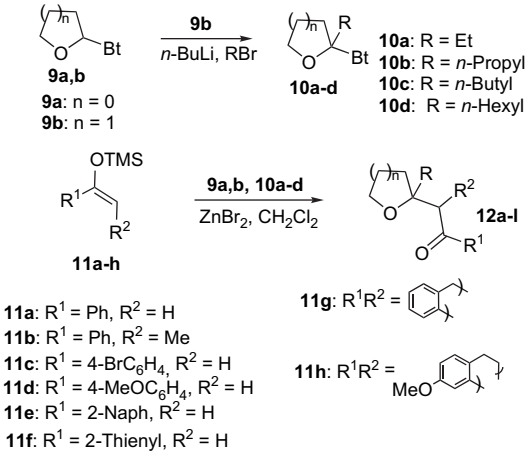


Scheme 2.



Scheme 3.

of acetals in Mukaiyama aldol-type reactions of silyl enol ethers **11** allows the preparation of β-alkoxy ketones **12** in good to excellent yields (Scheme 4 and Table 1).



Scheme 4. For designation of R, R^1, and R^2 in **11** and **12**, see Table 1.

Bt–C–O compounds **1** are readily available,[7c,18] and stable (shelf life more than 8 months). Colorless viscous liquids **9a**,**b** were prepared in 95–100% yields as mixtures of benzotriazol-1-yl and -2-yl isomers by the addition of benzotriazole to 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran, respectively, in CCl_4.[18]

Earlier reports from our laboratory suggested that lithio-derivatives **1** (R^1=Li) could not be generated unless R^2=hetero(aromatic),[7c] alkenyl,[7a] alkynyl,[7b] or R^3=aryl.[7d] Rather surprisingly we now find that treatment of **9b** with 1.2 M equiv of *n*-BuLi at −78 °C and then quenching the resultant carbanion with a series of alkyl bromides provides the alkylated products **10a–d** in 40–90% yields. The structures of **10a–d** were confirmed by their spectral data together with elemental analyses or HRMS.

The aldol-type reaction of silyl enol ether **11a** with **9a** in CH_2Cl_2 with 2 M equiv of $ZnBr_2$ under reflux proceeded smoothly to provide 1-phenyl-2-(tetrahydrofuran-2-yl)-ethanone (**12a**) (86%). No product was obtained with $(CH_3)_3SiOTf$ at −78 °C to reflux, $TiCl_4$ at −78 °C to rt, or $AlCl_3$ at rt to reflux. Silyl enol ethers **11a–h** reacted with **9a**,**b** or **10a–d** under the same reaction conditions to give

Table 1. Synthesis of α-substituted ketones **12a–l**

Start **11**	Product **12**	*n*	R	R^1	R^2	Yield (%)
11a	**12a**	0	H	Ph	H	86
11e	**12b**	1	H	2-Naph	H	71
11c	**12c**	0	H	4-BrC_6H_4	H	80
11f	**12d**	0	H	2-Thienyl	H	65
11b	**12e**	0	H	Ph	Me	79[b]
11f	**12f**	0	H	[a]		91
11g	**12g**	1	H	[a]		80[c]
11b	**12h**	1	H	Ph	Me	92[d]
11e	**12i**	1	*n*-Pr	2-Naph	H	60
11f	**12j**	1	*n*-Bu	2-Thienyl	H	62
11d	**12k**	1	Et	4-$MeOC_6H_4$	H	65
11f	**12l**	1	*n*-Hex	2-Thienyl	H	65

[a] See Scheme 4.
[b] Isolated as diastereoisomeric mixture in a 2:1 ratio.
[c] Isolated as diastereoisomeric mixture in a 3:1 ratio.
[d] Isolated as diastereoisomeric mixture in a 1:1 ratio.

β-alkoxy ketones **12b–l** in yields ranging from 60 to 92% (Scheme 4 and Table 1).

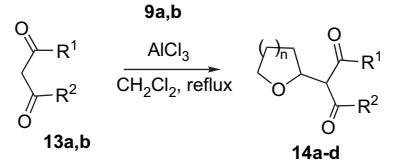
Although the reactions of **9a**,**b** and **10a–d** with **11a–h** were structurally tolerant for the silyl enol ether component, some failures were noted. Silyl enol ether **11a** gave no product with 1-(ethoxy-1-benzotriazolylethane, 1-(ethoxy-naphthalen-2-yl-methyl)benzotriazole, 1-(1-methoxy-1-phenylethyl)-1-benzotriazole, or 1-(1-ethoxy-1-methyl-3-phenylprop-2-ynyl)benzotriazole.

The present approach for the preparation of α-substituted ketones **12** utilizes inexpensive Lewis acid under mild conditions and shows good generality for silyl enol ethers prepared from acyclic (to give **12a–c**,**e**,**h**,**i**,**k**), cyclic (to give **12f** and **g**), and heteroaromatic ketones (**12d**,**j** and **l**). The required benzotriazolylalkyl alkyl ethers type **9a**,**b** and **10a–d** are easily prepared and stable alkoxyalkylation reagents are more convenient than the acetal analogs. Our new methodology provided a wide range of α-substituted ketones **12** bearing a tetrahydrofuran or tetrahydropyran unit at positions in which they are structural subunits in many naturally occurring nucleosides, glycolipids, polyether antibiotics, and pheromones.[19]

2.2. α-Alkoxyalkylations of 1,3-dicarbonyl compounds

Enolizable diketones can bind to both metal ions[20] and nonmetallic elements,[21] and are used as subunits in supramolecular host molecules.[22] Previous α-alkoxyalkylations of 1,3-dicarbonyl compounds **13** have usually involved either (i) treatment of chloromethyl methyl ether with organometallic derivatives of **13**[23] (but this is limited to methoxymethylation and α-chloro ethers, which are cancerogenic); (ii) addition of active methylenes to cyclic enol ethers employing $AuCl_3$/AgOTf as a catalyst[24] (limited to diketones and requires expensive reagents); or (iii) Lewis acid-induced alkoxyalkylation of **13** with acetal[25] (valuable only to prepare particular analogs of **13**). We now report the use of of 1-benzotriazolylalkyl alkyl ethers **9a**,**b** as alkoxyalkylating reagents for converting **13** into alkoxyalkylated products **14**.

Trials with different Lewis acids revealed that 2.0 M equiv of $AlCl_3$ catalyzed the stoichiometric reaction of dimethyl malonate **13b** with **9a** to provide 79% of **14c**. The α-alkoxyalkylation reaction also gave **14a**,**b** derived from β-keto ester and **14d** from malonate (Scheme 5 and Table 2). All reactions proceeded smoothly to give the corresponding condensation products **14a–d**. The NMR of the crude products shows that benzotriazole is usually the only byproduct, although adducts **14** are occasionally contaminated by a small amount of unreacted **13**. Success with 1,3-dicarbonyl



Scheme 5. For designation of R^1 and R^2 in **14**, see Table 2.

Table 2. Alkoxyalkylations of 1,3-dicarbonyl compounds

Compd	*n*	R^1	R^2	Yield (%)
14a	0	Ph	OEt	67
14b	1	Ph	OEt	62[a]
14c	0	OMe	OMe	79
14d	1	OMe	OMe	88

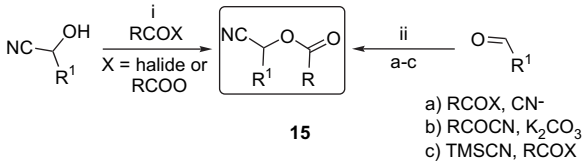
[a] Total yield of two isolated diastereoisomers in a 1:1.2 ratio.

compounds demonstrates the general applicability of this synthetic route and provided the previously unreported analogs **14a–d** in yields ranging from 62 to 88%.

However attempts to react Bt–C–O compounds of type **9** or **10** with organostannanes, amines, thiols, phenols, allyl trimethylsilane, terminal alkenes, aromatics, and heteroaromatics failed.

2.3. Synthesis of cyanohydrin esters

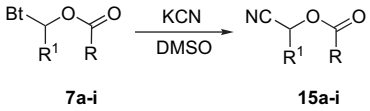
Cyanohydrins are of interest as pesticides,[26] and synthetic precursors.[27] Cyanohydrin esters **15** are versatile synthetic intermediates.[28] Approaches for cyanohydrin esters include (Scheme 6): (i) acylation of cyanohydrins with the appropriate acyl halide or acid anhydride;[27a] (ii) cyanoacylation of aldehydes by (a) acyl halides in aqueous cyanide solution,[29] (b) acyl cyanides in aqueous K_2CO_3 solution,[30] or (c) trimethylsilyl cyanide and acid anhydride under the influence of iron(III) chloride.[31] Method (ii)b is commonly used for the synthesis of the title compounds, however, acyl cyanides are susceptible to hydrolysis and particularly aliphatic aldehydes having α-hydrogen atom readily undergo aldol condensation under alkaline conditions. Consequently, a number of modifications for method iic have been proposed. For example, phase-transfer catalyst[32] and Bu_3SnCN have been utilized for the addition of acyl cyanide to aldehydes.[33] We now report for acylated cyanohydrin **15** from 1-(benzotriazol-1-yl)alkyl esters **7** with cyanide without catalyst (Scheme 6).



Scheme 6.

1-(Benzotriazol-1-yl)alkyl esters **7** were prepared by treating 1-(benzotriazol-1-yl)-1-chloroalkanes with sodium carboxylates for **7a**,**b**[8] or by *O*-acylation of aldehydes with *N*-acylbenzotriazoles in the presence of K_2CO_3 for **7c–g**.[34] Our treatment of **7a** with 2 M equiv of KCN in DMSO at rt afforded 97% of cyanomethyl benzoate (**15a**). Similarly, 1-(benzotriazol-1-yl)alkyl esters **7a–j** were reacted with KCN to provide the expected cyanohydrin esters **15b–j** in 55–98% yields (Scheme 7 and Table 3). This approach improved the previously reported yield[30a] of compound **15e** from 49 to 80%, and afforded **15a**[35] and **15c**[30b] in yields comparable to the literature. The structures of all final products obtained have been confirmed by ^1H and ^{13}C NMR data and elemental analyses. Data for known

compounds **15a**,**c**,**e** have been compared with those available in the literature.



7a-i **15a-i**

Scheme 7. For designation of R and R^1 in **15**, see Table 3.

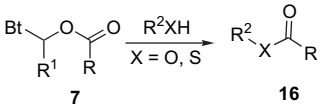
Table 3. Synthesis of cyanohydrin esters **15a–i**

Compd	R	R^1	Yield (%)
15a	Ph	H	98 (97[a])[35]
15b	Ph	*t*-BuCH_2	87
15c	Ph	*n*-Pr	95 (94[a])[30b]
15d	Ph	Et	89
15e	Ph	Ph	80 (49[a])[30a]
15f	*t*-Bu	3,4,5-$(MeO)_3C_6H_2$	82
15g	*t*-Bu	*n*-Pr	96
15h	2-Thienyl	*n*-Pr	92
15i	2-Furyl	*t*-BuCH_2	85

[a] Literature yield.

Our approach allows the preparation of a variety of alkanoylated, aryolated or heteroaryolated cyanohydrins derived from (i) formaldehyde **9a**, which is inaccessible from acyl cyanides and aldehydes by the reported methods,[27a,29,30a,b,31–33] (ii) aliphatic **9b–d** and **9g–i**, or (iii) aromatic aldehydes **9e**,**f**; the process requires mild conditions with no catalyst.

Reactions of **7** with alcohols, thiols, or organosilanes failed to provide the corresponding acyloxyalkylation products. Instead, with alcohols or thiols we obtained ester or thioester derivatives **16**, respectively, in quantitative yields (Scheme 8).



7 **16**

Scheme 8.

3. Summary

In summary, novel and convenient routes have been developed for the preparation of a wide range of ketones **12**, β-keto esters **14a**,**b**, and malonates **14c**,**d** bearing tetrahydrofuran or tetrahydropyran structural units at the α position. Compared to acetal analogs,[38] our use of α-benzotriazolylalkyl ethers is advantageous since it requires inexpensive Lewis acids and with benzotriazole adducts it is applicable not only when R=H but also when R=alkyl.

Reactions of easily prepared 1-(benzotriazol-1-yl)alkyl esters **7** with cyanide anion give acylated cyanohydrins **15**. The method utilizes nontoxic, and recyclable benzotriazole as an auxiliary to provide α-cyano aliphatic-, aromatic-, and heteroaromatic esters. In terms of yields, generality, and experimental simplicity, the conversion of **7** to **15** represents an attractive alternative to earlier methods for synthesizing acylated cyanohydrins.[27a,29,30a,b,31–33]

4. Experimental

4.1. General methods

Melting points were determined on a capillary point apparatus equipped with a digital thermometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300 MHz NMR spectrometer in $CDCl_3$ unless stated. Column chromatography was performed on silica gel 200–425 mesh. THF was distilled from sodium-benzophenone ketyl and CH_2Cl_2 was dried over molecular sieves prior to use. 1-(α-Alkoxyalkyl)benzotriazoles **10a**,**b**[18] were prepared according to literature procedures. 1-(Benzotriazol-1-yl)alkyl esters **7a**,**b**[8] and **7c–g**[34] were prepared following literature procedures.

4.2. General procedure for the preparation of 1-(α-alkoxyalkyl)benzotriazoles 10a–d

To a solution of **9b** (0.408 g, 2 mmol) in dry THF (5 mL), 1.1 equiv of *n*-BuLi (1.4 mL, 1.6 M in pentane, 2.2 mmol) was added at −78 °C. The solution was stirred at −78 °C for 1 h, and the appropriate alkyl halide (2 mmol) was added. The reaction mixture was stirred for 10 h while the temperature was allowed to rise to 20 °C. After quenching with water (5 mL) and extraction with EtOAc (3×20 mL), the combined organic layers were washed with water (25 mL), dried over $MgSO_4$, and the solvent was removed in vacuo. The resultant oil was subjected to column chromatography (eluent: ethyl acetate/hexanes=1:10 then 1:5) to give the pure product.

4.2.1. 1-(2-Ethyltetrahydropyran-2-yl)-1*H*-benzotriazole (10a). Colorless oil (40%). ^1H NMR δ 8.07 (d, J=8.2 Hz, 1H), 7.90 (d, J=8.4 Hz, 1H), 7.44 (ddd, J=15.2, 7.0, 1.1 Hz, 1H), 7.36 (ddd, J=15.2, 8.1, 1.1 Hz, 1H), 3.89–3.84 (m, 1H), 3.29–3.25 (m, 1H), 3.15 (td, J=11.8, 2.6 Hz, 1H), 2.15–1.88 (m, 2H), 1.86–1.71 (m, 4H), 1.47–1.40 (m, 1H), 0.68 (t, J=7.6 Hz, 3H). ^{13}C NMR δ 146.6, 132.2, 127.1, 123.8, 119.7, 113.0, 94.1, 63.4, 35.2, 30.6, 24.2, 18.6, 7.4. Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.65; H, 7.71; N, 18.03.

4.2.2. 1-(2-Propyltetrahydropyran-2-yl)-1*H*-benzotriazole (10b). Colorless oil (60%). ^1H NMR δ 8.07 (d, J=8.2 Hz, 1H), 7.90 (d, J=8.4 Hz, 1H), 7.44 (ddd, J=15.2, 7.0, 1.0 Hz, 1H), 7.36 (ddd, J=15.2, 7.1, 1.0 Hz, 1H), 3.88–3.83 (m, 1H), 3.29–3.24 (m, 1H), 3.14 (td, J=11.9, 2.5 Hz, 1H), 2.08–1.66 (m, 7H), 1.46–1.27 (m, 2H), 0.92–0.81 (m, 1H), 0.74 (t, J=7.1 Hz, 3H). ^{13}C NMR δ 146.5, 132.2, 127.1, 123.7, 119.6, 112.9, 93.7, 63.3, 44.6, 31.2, 24.1, 18.6, 16.2, 13.8. HRMS: m/z $[M+H]^+$ calcd for $C_{14}H_{19}N_3O$: 246.16009; found: 246.16247.

4.2.3. 1-(2-Butyltetrahydropyran-2-yl)-1*H*-benzotriazole (10c). Colorless oil (90%). ^1H NMR δ 8.06 (d, J=8.2 Hz, 1H), 7.90 (d, J=8.2 Hz, 1H), 7.44 (ddd, J=15.2, 7.0, 1.1 Hz, 1H), 7.36 (ddd, J=15.2, 8.2, 1.1 Hz, 1H), 3.88–3.83 (m, 1H), 3.29–3.25 (m, 1H), 3.14 (td, J=11.8, 2.6 Hz, 1H), 2.10–1.66 (m, 7H), 1.50–1.23 (m, 2H), 1.18–1.08 (m, 2H), 0.74 (t, J=7.3 Hz, 3H). ^{13}C NMR δ 146.5, 132.2, 127.1, 123.7, 119.6, 112.9, 93.7, 63.3, 42.1, 31.2, 24.9,

24.1, 22.4, 18.6, 13.7. HRMS: *m/z* [M+Na]$^+$ calcd for $C_{15}H_{21}N_3O$: 282.15768; found: 282.15996.

4.2.4. 1-(2-Hexyltetrahydropyran-2-yl)-1*H*-benzotriazole (10d). Colorless oil (80%). ^{1}H NMR δ 8.07 (d, J=8.2 Hz, 1H), 7.90 (d, J=8.2 Hz, 1H), 7.44 (ddd, J=15.2, 7.0, 1.0 Hz, 1H), 7.35 (ddd, J=15.2, 8.1, 0.8 Hz, 1H), 3.88–3.83 (m, 1H), 3.29–3.25 (m, 1H), 3.14 (td, J=11.8, 2.6 Hz, 1H), 2.10–1.70 (m, 6H), 1.46–1.21 (m, 2H), 1.20–1.14 (m, 2H), 1.11–1.07 (m, 5H), 0.77 (t, J=7.0 Hz, 3H). ^{13}C NMR δ 146.5, 132.1, 127.0, 123.7, 119.6, 112.9, 93.7, 63.3, 42.3, 31.3, 31.1, 28.9, 27.3, 24.1, 22.7, 22.3, 18.6, 13.8. Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77; N, 14.62. Found: C, 70.71; H, 9.08; N, 14.82.

4.3. General procedure for the preparation of β-alkoxy ketones 12a–l

To a stirred solution of silyl enol ether **11** (1 mmol) and 1-(α-alkoxyalkyl)benzotriazoles **9a**,**b** or **10a**–**d** (1 mmol) in dry dichloromethane (40 mL) was added $ZnBr_2$ (0.495 g, 2.2 mmol) under nitrogen atmosphere at rt. The mixture was refluxed for 8 h, and was monitored by TLC. Ether (100 mL) was added, and the solution was washed with cold water (3×25) and dried over $MgSO_4$. After removal of the solvent in vacuo, the resulting crude product was purified by column chromatography on silica gel and eluted with 9/1 hexanes/EtOAc to give the pure product **12**. Structures of **12a**–**l** were supported by their ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectra no longer showed distinctive signals in the range 7.0–8.2 ppm corresponding to the benzotriazolyl group. Similarly, ^{13}C NMR of **12a**–**l** showed new signals at 196.0–199.6 ppm assignable to carbonyl carbon and no longer showed the characteristic benzotriazole signals around 110, 120, and 146 ppm.

4.3.1. 1-Phenyl-2-(tetrahydrofuran-2-yl)ethanone (12a). Colorless oil[36] (86%). ^{1}H NMR δ 7.96 (d, J=7.3 Hz, 2H), 7.58–7.53 (m, 1H), 7.48–7.43 (m, 2H), 4.44 (pentet, J=6.6 Hz, 1H), 3.93–3.85 (m, 1H), 3.78–3.71 (m, 1H), 3.39 (dd, J=16.2, 6.0 Hz, 1H), 3.06 (dd, J=16.5, 6.6 Hz, 1H), 2.19 (sextet, J=6.3 Hz, 1H), 1.97–1.87 (m, 2H), 1.62–1.50 (m, 1H). ^{13}C NMR δ 198.3, 136.9, 133.0, 128.5, 128.1, 75.3, 67.7, 44.5, 31.5, 25.5.

4.3.2. 1-Naphthalen-2-yl-2-(tetrahydropyran-2-yl)ethanone (12b). Colorless oil (89%). ^{1}H NMR δ 8.47 (s, 1H), 8.03 (d, J=8.4 Hz, 1H), 7.95 (d, J=7.8 Hz, 1H), 7.88–7.83 (m, 2H), 7.60–7.50 (m, 2H), 4.05–3.94 (m, 2H), 3.52–3.39 (m, 2H), 3.03 (dd, J=15.9, 5.7 Hz, 1H), 1.87–1.76 (m, 2H), 1.62–1.38 (m, 4H). ^{13}C NMR δ 198.2, 135.5, 134.5, 132.4, 130.0, 129.5, 128.4, 128.3, 127.6, 126.6, 123.9, 74.4, 68.6, 45.3, 31.9, 25.8, 23.3. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.16; H, 7.06.

4.3.3. 1-(4-Bromophenyl)-2-(tetrahydrofuran-2-yl)ethanone (12c). Gray prisms (80%), mp 40–41 °C. ^{1}H NMR δ 7.83 (d, J=8.5 Hz, 2H), 7.60 (d, J=8.5 Hz, 2H), 4.43–4.34 (m, 1H), 3.92–3.85 (m, 1H), 3.79–3.71 (m, 1H), 3.34 (dd, J=16.2, 6.3 Hz, 1H), 3.02 (dd, J=19.2, 9.3 Hz, 1H), 2.25–2.14 (m, 1H), 1.98–1.88 (m, 2H), 1.67–1.50 (m, 1H). ^{13}C NMR δ 197.4, 135.7, 131.9, 129.7, 128.3, 75.3, 67.9, 44.6, 31.6, 25.6. Anal. Calcd for $C_{12}H_{13}BrO_2$: C, 53.55; H, 4.87. Found: 53.57; H, 4.78.

4.3.4. 2-(Tetrahydrofuran-2-yl)-1-thiophen-2-ylethanone (12d). Yellow Oil (65%). ^{1}H NMR δ 7.74 (d, J=3.7 Hz, 1H), 7.65 (d, J=4.8 Hz, 1H), 7.14 (t, J=4.3 Hz, 1H), 4.45–4.35 (m, 1H), 3.94–3.85 (m, 1H), 3.79–3.72 (m, 1H), 3.35–3.26 (m, 1H), 3.03–2.59 (m, 1H), 2.23–2.13 (m, 1H), 1.98–1.90 (m, 2H), 1.67–1.62 (m, 1H). ^{13}C NMR δ 191.2, 144.6, 133.8, 132.3, 128.1, 75.5, 67.9, 45.3, 31.5, 25.6. Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 60.88; H, 6.28.

4.3.5. 1-Phenyl-2-(tetrahydrofuran-2-yl)-propan-1-one (12e) [two diastereoisomers 2:1]. Yellow oil (79%). ^{1}H NMR δ 8.00–7.96 (m, 2H), 7.59–7.52 (m, 1H), 7.49–7.43 (m, 2H), 4.22–4.09 (m, 1H), 3.87–3.72 (m, 2H), 3.69–3.55 (m, 1H), 2.08–1.98 (m, 1H), 1.96–1.80 (m, 2H), 1.70–1.45 (m, 1H), 1.32 (d, J=7.0 Hz, 2H), 1.16 (d, J=6.9 Hz, 1H). ^{13}C NMR δ 203.1, 203.0, 137.0, 136.8, 133.0, 132.8, 128.6, 128.5, 128.4, 128.3, 81.0, 80.9, 68.1, 67.8, 45.8, 45.7, 29.7, 29.1, 25.7, 25.6, 15.4, 13.8. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.20; H, 8.18.

4.3.6. 2-(Tetrahydrofuran-2-yl)indan-1-one (12f). Yellow oil (91%). ^{1}H NMR δ 7.75 (d, J=7.8 Hz, 1H), 7.61–7.57 (m, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.39–7.34 (m, 1H), 4.37–4.28 (m, 1H), 3.93–3.83 (m, 1H), 3.80–3.71 (m, 1H), 3.31–3.15 (m, 2H), 3.01 (dd, J=17.1, 2.7 Hz, 1H), 1.97–1.79 (m, 3H), 1.62–1.54 (m, 1H). ^{13}C NMR δ 206.4, 154.2, 137.3, 134.7, 127.2, 126.4, 123.7, 79.2, 68.3, 50.1, 29.0, 26.8, 25.8. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.00; H, 7.39.

4.3.7. 7-Methoxy-2-(tetrahydropyran-2-yl)-3,4-dihydro-2*H*-naphthalen-1-one (12g) [two diastereoisomers 3:1]. Yellow oil (80%). ^{1}H NMR δ 7.98 (dd, J=8.7, 1.7 Hz, 1H), 6.79 (dt, J=8.6, 2.6 Hz, 1H), 6.67 (s, 1H), 4.12–3.91 (m, 2H), 3.83 (s, 3H), 3.57–3.42 (m, 1H), 3.04–2.81 (m, 2H), 2.72 (dt, J=12.4, 4.1 Hz, 0.5H), 2.41–2.14 (m, 2H), 2.01–1.83 (m, 1.5H), 1.58–1.49 (m, 5H). ^{13}C NMR δ 196.9, 196.5, 163.3, 146.6, 146.5, 129.8, 129.6, 126.4, 126.3, 112.9, 112.9, 112.3, 112.2, 76.6, 75.1, 68.9, 68.7, 55.3, 55.2, 52.4, 52.3, 29.6, 29.3, 28.4, 26.6, 26.0, 25.9, 23.9, 23.5, 23.4, 23.2. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.44; H, 8.10.

4.3.8. 1-Phenyl-2-(tetrahydropyran-2-yl)-propan-1-one (12h) [two diastereoisomers 1:1]. Colorless oil (92%). ^{1}H NMR δ 8.00–7.94 (m, 2H), 7.57–7.41 (m, 3H), 4.02–3.97 (m, 0.5H), 3.85–3.81 (m, 0.5H), 3.73–3.66 (m, 0.5H), 3.63–3.52 (m, 1.5H), 3.45–3.32 (m, 1H), 1.89–1.85 (m, 0.5H), 1.76–1.72 (m, 1H), 1.61–1.43 (m, 3.5H), 1.34–1.20 (m, 2.5H), 1.10 (d, J=6.9 Hz, 1.5H). ^{13}C NMR δ 203.7, 202.9, 137.2, 136.9, 132.8, 132.6, 128.4, 128.3, 128.3, 128.2, 79.7, 79.2, 68.6, 68.4, 46.1, 45.9, 29.8, 28.5, 25.9, 25.8, 23.2, 23.2, 14.3, 13.2. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.27; H, 8.61.

4.3.9. 1-Naphthalen-2-yl-2-(2-propyltetrahydropyran-2-yl)ethanone (12i). Yellow oil (60%). ^{1}H NMR δ 8.51 (s, 1H), 8.04 (dd, J=8.6, 1.6 Hz, 1H), 7.97–7.92 (m, 1H), 7.88–7.85 (m, 2H), 7.61–7.51 (m, 2H), 3.69 (t, J=5.4 Hz, 2H), 3.34 (dd, J=27.7, 15.2 Hz, 2H), 1.90–1.59 (m, 6H),

1.56–1.48 (m, 2H), 1.44–1.26 (m, 2H), 0.89 (t, J=7.3 Hz, 3H). ^{13}C NMR δ 198.9, 135.7, 135.4, 132.5, 130.0, 129.6, 128.3, 128.2, 127.7, 136.6, 124.0, 75.4, 61.4, 44.7, 36.7, 33.5, 25.7, 19.0, 16.3, 14.5. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.86; H, 7.86.

4.3.10. 2-(2-Butyltetrahydropyran-2-yl)-1-thiophen-2-yl-ethanone (12j). Brown oil (62%). ^{1}H NMR δ 7.74 (dd, J=3.8, 1.0 Hz, 1H), 7.63–7.61 (m, 1H), 7.12 (dd, J=4.9, 3.8 Hz, 1H), 3.67 (t, J=5.4 Hz, 2H), 3.12 (AB system, J_{AB}=33.0, 14.7 Hz, 2H), 1.89–1.75 (m, 1H), 1.73–1.58 (m, 5H), 1.55–1.49 (m, 2H), 1.35–1.27 (m, 4H), 0.88 (t, J=7.0 Hz, 3H). ^{13}C NMR δ 191.7, 146.1, 133.7, 132.3, 128.0, 75.1, 61.4, 45.8, 34.2, 33.4, 25.6, 25.2, 23.1, 19.0, 14.1. Anal. Calcd for $C_{15}H_{22}NO_2S$: C, 67.63; H, 8.32. Found: C, 67.79; H, 8.63.

4.3.11. 2-(2-Ethyltetrahydropyran-2-yl)-1-(4-methoxyphenyl)ethanone (12k). Colorless oil (65%). ^{1}H NMR δ 7.99–7.95 (m, 2H), 6.95–6.90 (m, 2H), 3.87 (s, 3H), 3.68–3.64 (m, 2H), 3.13 (dd, J=32.3, 15.0 Hz, 2H), 1.94–1.86 (m, 1H), 1.75–1.61 (m, 5H), 1.53–1.48 (m, 2H), 0.87 (t, J=7.5 Hz, 3H). ^{13}C NMR δ 197.6, 163.2, 131.5, 130.6, 113.5, 75.4, 61.3, 55.4, 43.9, 33.1, 26.7, 25.7, 19.0, 7.4. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.07; H, 8.83.

4.3.12. 2-(2-Hexyltetrahydropyran-2-yl)-1-thiophen-2-yl-ethanone (12l). Brown oil (65%). ^{1}H NMR δ 7.74 (dd, J=3.8, 1.0 Hz, 1H), 7.62 (dd, J=4.9, 1.0 Hz, 1H), 7.12 (dd, J=4.9, 3.9 Hz, 1H), 3.67 (t, J=5.4 Hz, 2H), 3.12 (AB system, J_{AB}=31.2, 14.4 Hz, 2H), 1.86–1.59 (m, 6H), 1.54–1.51 (m, 2H), 1.36–1.26 (m, 8H), 0.86 (t, J=6.7 Hz, 3H). ^{13}C NMR δ 191.6, 146.1, 133.7, 132.3, 128.0, 75.1, 61.4, 45.8, 34.5, 33.4, 31.8, 29.7, 25.6, 22.9, 22.6, 19.0, 14.1. Anal. Calcd for $C_{17}H_{26}NO_2S$: C, 69.34; H, 8.90. Found: C, 69.25; H, 9.24.

4.4. General procedure for 14

To a stirred solution of 1,3-dicarbonyl compound **13** (2 mmol) and 1-(α-alkoxyalkyl)benzotriazoles **9a**,**b** (2 mmol) in dry dichloromethane (40 mL), anhydrous $AlCl_3$ (0.534 g, 4 mmol) was added portion-wise under nitrogen atmosphere at rt over a period of 5 min. The mixture was then heated under reflux, monitored by TLC and continued for 8 h. Ether (100 mL) was added and the solution was washed with cold water (3×25) and dried over $MgSO_4$. After removal of the solvent in vacuo, the resulting crude product was purified by column chromatography on silica gel and eluted with hexanes/EtOAc 9:1 to give **14**.

4.4.1. 3-Oxo-3-phenyl-2-(tetrahydrofuran-2-yl)-propionic acid ethyl ester (14a). Colorless oil (67%). ^{1}H NMR δ 8.05–8.01 (m, 2H), 7.62–7.56 (m, 1H), 7.51–7.45 (m, 2H), 4.74–4.64 (m, 1H), 4.43 (dd, J=13.2, 9.1 Hz, 1H), 4.21–4.11 (m, 2H), 3.92–3.69 (m, 2H), 2.26–2.15 (m, 1H), 1.99–1.84 (m, 2H), 1.57–1.48 (m, 1H), 1.21–1.14 (m, 3H). ^{13}C NMR δ 193.6, 193.2, 167.9, 167.5, 136.7, 136.3, 133.7, 133.4, 128.8, 128.7, 128.6, 78.0, 77.7, 68.1, 68.0, 61.6, 61.4, 60.1, 59.3, 30.2, 29.9, 25.4, 25.4, 13.9, 13.9. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.37; H, 7.20.

4.4.2. 3-Oxo-3-phenyl-2-(tetrahydropyran-2-yl)propionic acid ethyl ester (14b) [two isolated diastereoisomers]. First diastereoisomer: colorless oil (28%). ^{1}H NMR δ 8.03–8.01 (m, 2H), 7.59–7.54 (m, 1H), 7.49–7.44 (m, 2H), 4.48 (d, J=9.3 Hz, 1H), 4.25–4.10 (m, 3H), 3.87–3.82 (m, 1H), 3.43 (td, J=11.1, 3.2 Hz, 1H), 1.89–1.80 (m, 2H), 1.69–1.32 (m, 4H), 1.81 (t, J=7.1 Hz, 3H). ^{13}C NMR δ 193.7, 167.1, 137.1, 133.3, 128.8, 128.6, 76.9, 68.7, 61.4, 59.8, 29.7, 25.7, 23.1, 14.0. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.59; H, 7.67. Second diastereoisomer: yellow oil (34%). ^{1}H NMR δ 8.06–8.03 (m, 2H), 7.62–7.57 (m, 1H), 7.50–7.45 (m, 2H), 4.46 (d, J=9.5 Hz, 1H), 4.26–4.10 (m, 3H), 4.03–3.98 (m, 1H), 3.51 (td, J=11.3, 2.9 Hz, 1H), 1.78–1.23 (m, 6H), 1.17 (t, J=7.1 Hz, 3H). ^{13}C NMR δ 192.6, 167.8, 136.4, 133.7, 128.7, 128.7, 77.1, 68.9, 61.4, 60.6, 29.8, 25.7, 23.0, 13.9. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.69; H, 7.63.

4.4.3. 3-Oxo-2-(tetrahydrofuran-2-yl)butyric acid methyl ester (14c). Colorless oil (79%). ^{1}H NMR δ 4.50–4.43 (m, 1H), 3.91–3.80 (m, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.49 (d, J=9.1 Hz, 1H), 2.23–2.12 (m, 1H), 1.97–1.88 (m, 2H), 1.78–1.66 (m, 1H). ^{13}C NMR δ 167.9, 167.5, 76.9, 68.3, 57.0, 52.6, 52.5, 29.9, 25.4. Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.09; H, 7.23.

4.4.4. 3-Oxo-2-(tetrahydropyran-2-yl)butyric acid methyl ester (14d). Colorless oil (79%). ^{1}H NMR δ 4.04–3.96 (m, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.61 (d, J=9.3 Hz, 1H), 2.31–2.18 (m, 1H), 1.94–1.70 (m, 3H), 1.65–1.53 (m, 2H), 1.45–1.24 (m, 2H). ^{13}C NMR δ 172.2, 171.5, 72.8, 60.3, 52.7, 52.5, 31.3, 30.4, 23.0, 22.0. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.84; H, 7.76.

4.5. General procedure for the preparation of cyanohydrin esters 15

A mixture of 1-(benzotriazol-1-yl)alkyl ester **7** (2 mmol) and potassium cyanide (0.13 g, 2 mmol) in DMSO (10 mL) was stirred for 4 h at 20 °C. The mixture was poured into water (40 mL) and extracted with ethyl acetate (3× 30 mL). The extracts were washed with water, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was placed in a silica gel column and eluted with hexanes/EtOAc 5:1 to give **15**. Structures **15a–d** were supported by their elemental analyses and spectral data. For example, in the ^{1}H NMR spectrum of **15c** a new multiplet appeared at 3.91–3.80 ppm, confirming the successful displacement of the benzotriazolyl group. Displacement of nitrogen (benzotriazolyl group) by carbon (dicarbonyl moiety) resulted in an upfield shift of the signal of the ethereal tertiary α-carbon atom (from 94.0, Bt^2, or 87.7, Bt^1 to 76.9 ppm) in the ^{13}C NMR spectrum of **15c**.

4.5.1. Benzoic acid cyanomethyl ester (15a). Colorless oil[35] (98%). ^{1}H NMR δ 8.07–8.04 (m, 2H), 7.66–7.61 (m, 1H), 7.51–7.46 (m, 2H), 4.96 (s, 1H). ^{13}C NMR δ 164.9, 134.1, 130.0, 128.6, 127.8, 114.5, 48.8. Anal. Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.03; H, 4.31; N, 8.72.

4.5.2. Benzoic acid 1-cyano-3,3-dimethylbutyl ester (15b). Colorless oil (87%). ^{1}H NMR δ 8.07–8.04 (m, 2H),

7.65–7.60 (m, 1H), 7.51–7.46 (m, 2H), 5.63 (dd, *J*=7.5, 6 Hz, 1H), 2.13–1.99 (m, 2H), 1.05 (s, 9H). ^{13}C NMR δ 164.9, 134.0, 130.0, 128.7, 128.4, 117.9, 59.4, 45.8, 30.3, 29.6. Anal. Calcd for $C_{14}H_{14}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.78; H, 7.59; N, 6.29.

4.5.3. Benzoic acid 1-cyanobutyl ester (15c). Colorless microcrystals[30b] (95%), mp 48–49 °C. ^{1}H NMR δ 8.06–8.04 (m, 2H), 7.64–7.59 (m, 1H), 7.49–7.44 (m, 2H), 5.58 (t, *J*=6.6 Hz, 1H), 2.07–1.99 (m, 2H), 1.66–1.56 (m, 2H), 1.03 (t, *J*=7.4 Hz, 3H). ^{13}C NMR δ 164.6, 133.8, 129.8, 128.5, 128.1, 116.9, 61.3, 34.2, 17.9, 13.2. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.83; H, 6.66; N, 7.05.

4.5.4. Benzoic acid 1-cyanopropyl ester (15d). Colorless oil[37] (98%). ^{1}H NMR δ 8.07–8.04 (m, 2H), 7.65–7.60 (m, 1H), 7.51–7.45 (m, 2H), 5.54 (t, *J*=6.5 Hz, 1H), 2.07 (q, *J*=7.2 Hz, 2H), 1.19 (t, *J*=7.4 Hz, 3H). ^{13}C NMR δ 164.7, 133.9, 129.8, 128.6, 128.2, 116.7, 62.6, 25.9, 8.9. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.71; H, 5.86; N, 7.71.

4.5.5. Benzoic acid cyanophenylmethyl ester (15e). Colorless microcrystals (80%), mp 52–53 °C (lit.[30a] mp 59 °C). ^{1}H NMR δ 8.08–8.05 (m, 2H), 7.64–7.59 (m, 3H), 7.49–7.44 (m, 5H), 6.68 (s, 1H). ^{13}C NMR δ 164.6, 134.1, 131.8, 130.4, 130.0, 129.3, 128.6, 128.0, 127.8, 116.2, 63.3. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.91; H, 4.79; N, 5.95.

4.5.6. 2,2-Dimethylpropionic acid cyano(3,4,5-trimethoxyphenyl)methyl ester (15f). Colorless microcrystals (82%), mp 86–87 °C. ^{1}H NMR δ 6.71 (s, 2H), 6.36 (s, 1H), 3.89 (s, 6H), 3.87 (s, 3H), 1.26 (s, 9H). ^{13}C NMR δ 176.2, 153.6, 139.2, 127.3, 116.2, 104.5, 62.7, 60.7, 56.1, 38.7, 26.7. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.22; H, 7.11; N, 4.23.

4.5.7. 2,2-Dimethylpropionic acid 1-cyanobutyl ester (15g). Colorless oil (96%). ^{1}H NMR δ 5.32 (t, *J*=6.7 Hz, 1H), 1.94–1.87 (m, 2H), 1.60–1.48 (m, 2H), 1.24 (s, 9H), 1.00 (t, *J*=7.4 Hz, 3H). ^{13}C NMR δ 176.6, 117.0, 60.7, 38.7, 34.1, 26.8, 17.9, 13.2. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.64; H, 9.70; N, 7.48.

4.5.8. Thiophene-2-carboxylic acid 1-cyanobutyl ester (15h). Colorless microcrystals (92%), mp 49–50 °C. ^{1}H NMR δ 7.87 (dd, *J*=3.8, 1.2 Hz, 1H), 7.66 (dd, *J*=4.9, 1.2 Hz, 1H), 7.15 (dd, *J*=4.8, 3.8 Hz, 1H), 5.56 (t, *J*=6.7 Hz, 1H), 2.05–1.98 (m, 2H), 1.68–1.55 (m, 2H), 1.03 (t, *J*=7.3 Hz, 3H). ^{13}C NMR δ 160.2, 134.8, 134.0, 131.3, 128.0, 116.7, 61.4, 34.2, 17.9, 13.3. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.58; H, 5.24; N, 6.70.

4.5.9. Furan-2-carboxylic acid 1-cyano-2,2-dimethylpropyl ester (15i). Colorless oil (85%). ^{1}H NMR δ 7.66 (d, *J*=0.83 Hz, 1H), 7.28 (d, *J*=3.6 Hz, 1H), 6.57 (dd, *J*=3.4, 1.6 Hz, 1H), 5.60 (dd, *J*=7.1, 6.0 Hz, 1H), 2.10–1.98 (m, 2H), 1.04 (s, 9H). ^{13}C NMR δ 156.5, 147.5, 142.8, 119.8, 117.4, 112.2, 59.0, 45.5, 30.1, 29.4. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.25; H, 6.98; N, 6.72.

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