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Article

A New Approach to the Cyanoacetic Ester Synthesis

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Apresenta-se uma abordagem potencialmente útil e altenativa à síntese tradicional do éster ciano-acético. Nesta versão, a alquilação é seguida de uma clivagem redutiva do grupo ciano promovida por iodeto de samário (II). Algumas das vantagem nítidas dessa abordagem são que o grupamento éster se mantém intacto não sendo hidrolisado ao ácido carboxílico correspondente e, portanto, que outros grupos funcionais poderão ser utilizados, uma vez que as condições reacionais são bastante suaves, praticamente neutras.

A potentially useful alternative to the traditional cyanoacetic ester synthesis has been devised. In this version of the synthesis, the alkylation process is followed by a samarium(II) iodide-promoted reductive cleavage of the cyano group. Perceived advantages of this approach are that the ester remains intact and is not hydrolyzed to the corresponding carboxylic acid, and that other functional groups can be tolerated under the mild, nearly neutral reaction conditions.

Keywords: *cyanoacetic ester synthesis, samarium(II) iodide, reduction, α-cyano ester*

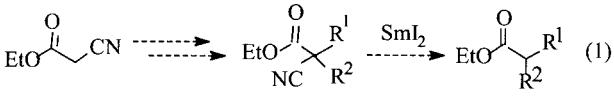
Introduction

The classic malonic ester synthesis provides a rapid, economical approach to simple, substituted carboxylic acids[1]. As a consequence, this process has become a mainstay of organic synthesis. In spite of its unqualified utility, this reaction and its progeny are not without some restrictions. The extreme pH conditions generally required for ester hydrolysis and decarboxylation creates limitations in the incorporation of other functional groups within the target structure. This limitation has prompted the development of several other very useful modifications. For example, the Krapcho protocol employs LiCl in wet DMSO to effect decarboxylation, but relatively high temperatures (140-180 °C) are required for the transformation[2].

Another very successful modification of the malonic ester synthesis for the generation of carboxylic acids is the cyanoacetic ester synthesis[3]. In this tranformation, ethyl cyanoacetate is alkylated to afford substituted a-cyano carboxylates, with subsequent aqueous hydrolysis and decarboxylation affording the desired carboxylic acid. Like the traditional malonic ester synthesis, this protocol does not remove the requirement for extreme pH because rather harsh conditions must still be employed for hydrolysis of the nitrile to a carboxylic acid.

A class of ketone syntheses related to the aforementioned carboxylic acid syntheses employs β-keto sulfoxides or β-keto sulfones as nucleophiles. Alkylation of these nucleophiles followed by a reductive desulfoxylation or desulfonylation (*e.g.*, with aluminum amalgam) provides the desired ketone[4]. The value of these methods is that the reductive cleavage reaction provides a mild, more pH neutral entry to ketones that would appear amenable to more highly functionalized systems.

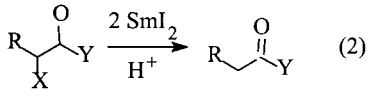
In this paper the concept of a reductive cleavage process to remove a cyano group is applied to alkylated ethyl cyanoacetate derivatives, providing a new alternative to the traditional cyanoacetic ester synthesis. Alkylation of ethyl cyanoacetate followed by a reductive cleavage of the cyano group with samarium(II) iodide (SmI_2) provides a novel approach to substituted esters that proceeds in generally high yields and can be carried out under conditions wherein esters, nitriles, halides, and amide functional groups survive (Eq. 1).



(1)

Results and Discussion

Samarium(II) iodide has gained a well-deserved reputation as a versatile, highly selective reductant in organic synthesis. Numerous functional groups can be reduced by this reagent, providing complementary reactivity patterns or selectivities when compared to many of the more traditional reductants[5]. Of particular relevance to the current discussion is the ability of SmI_2 to reduce a variety of α-heterosubstituted carbonyl substrates. As depicted in Eq. 2, a variety of heterosubstituents adjacent to carbonyl functional groups can be reductively cleaved under mild, essentially neutral conditions.



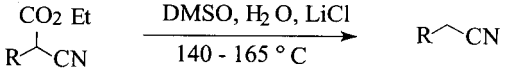
(2)

X = OH, OR', O_2CR', halide, $OSiR_3'$
OTs, SAr, S(O)Ar, SO_2 Ar, $OP(O)(OR')_2$
Y = R, OR'

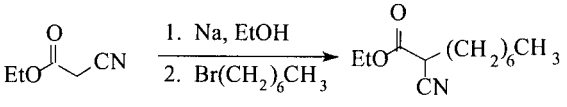
Although not previously reported, the reductive cleavage of α-cyano carbonyl substrates seemed feasible because the "pseudo-halide" character of the nitrile functional group should make it a good leaving group. Furthermore, nitriles are not competitively reduced by SmI_2. This reductive cleavage, when combined with the alkylation of ethyl cyanoacetate, would form the basis for a novel approach to the cyanoacetic ester synthesis which has the potential to provide a simple and convenient route to more highly functionalized esters. Described below are our efforts to bring about this transformation.

Substrates for the study were prepared by standard alkylation procedures commonly utilized in the traditional cyanoacetic ester synthesis. Thus, ethyl 2-cyanononanoate (1) was synthesized by alkylation of ethyl cyanoacetate (Eq. 3). 3-Oxooctanenitrile (2) was prepared from hexanoyl chloride via the corresponding Weinreb's amide (Eq. 4). Ethyl 2-cyano-2-methyl-3-phenylpropionate (3) was prepared by double alkylation of ethyl cyanoacetate (Eq. 5), and substrates 4 through 7 were prepared by alkylation of 1 (Eq. 6).

With the substrates in hand, the critical second step of the process was examined (Table 1). Each cyano ester was treated with SmI_2 in THF/EtOH/HMPA at 0 °C until the starting material disappeared. In each case, rapid disappearance of the starting material led to isolation of the desired esters in modest to high yields. A notable feature of the reaction is that, like the Krapcho decarboxylative procedure, the ester functional group remains intact during the synthesis and is not converted to a carboxylic acid (entry 1). Interestingly, the method is complementary to the Krapcho method in that the latter results in the formation of nitriles when applied to alkylated cyanoacetic ester substrates (Eq. 7).



In addition to the ester in the cyanoacetate moiety, remote esters incorporated in the alkylation process also remain intact



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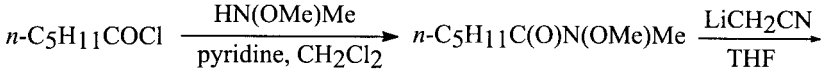

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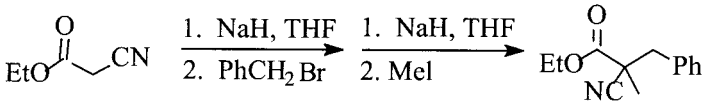

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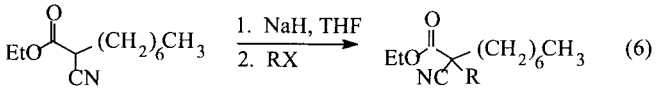
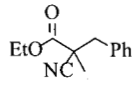
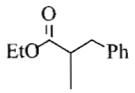
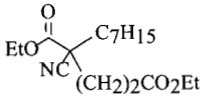
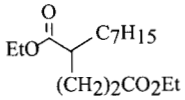
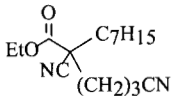
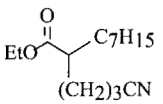
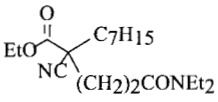
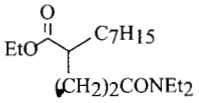
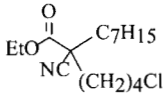
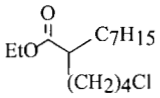


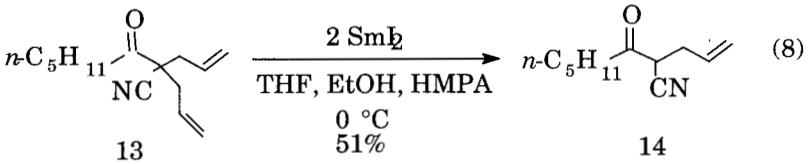
(6)

1 4-7

R = $(CH_2)_2CO_2Et$, $(CH_2)_3CN$, $(CH_2)_2CONEt_2$, $(CH_2)_4Cl$

Table 1. Reductive Cleavage of α-Cyano Esters using Samarium (II) Iodice.

Entry	Substrate	Product	% Isolated Yield
1	 **3**	 **8**	80
2	 **4**	 **9**	75
3	 **5**	 **10**	85
4	 **6**	 **11**	88
5	 **7**	 **12**	61



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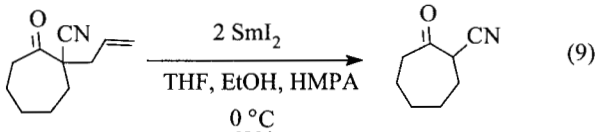

15 16 (9)

during the reductive decyanation reaction (entry 2). Similarly, nitriles, amides, and chlorides are well-tolerated under the mild reaction conditions (entries 3-5).

There are some limitations to this method. For example, epoxides and sulfones incorporated within the substrate undergo competitive reaction with the SmI_2, and therefore cannot be tolerated. Furthermore, alkylated cyanoketones in general provide poor yields of the desired product, perhaps due to competitive reduction of the ketone subsequent to reductive decyanation. Interestingly, allylated cyanoketones undergo reductive elimination of the allyl group, with allyl anion serving as the leaving group in preference to cyanide (Eqs. 8 and 9).

In summary, a potentially useful alternative to the traditional cyanoacetic ester synthesis has been devised. In this version of the synthesis, the alkylation process is followed by a SmI_2-promoted reductive cleavage of the cyano group. Perceived advantages of this approach are that the ester remains intact and is not hydrolyzed to the corresponding carboxylic acid, and the fact that other functional groups can be tolerated under the mild, nearly neutral reaction conditions.

Experimental

Ethyl 2-Cyano-nonanoate (1)

To 76 mL of dry EtOH at 0 °C was slowly added sodium metal (4.35 g, 189.6 mmol) with stirring. After all of the sodium had reacted, ethyl cyanoacetate (43.6 g, 385 mmol) was slowly added. The reaction mixture was stirred at 0 °C for 10 min, and then 1-bromoheptane (34.2 g, 191 mmol) was slowly added. The solution was then heated to reflux for twenty hours, then cooled to room tempertaure and quenched with 75 mL of 0.2 M HCl. The mixture was diluted with Et_2O, then washed with brine. The aqueous layers were extracted with Et_2O, and the combined organic extracts were dried over anhydrous $MgSO_4$. The product was subjected to flash chromatography in 5:1 hexanes/EtOAc. The product was then distilled (short path) to provide a colorless oil (23.41 g, 110.9 mmol, 59%): bp 68-72 °C/0.1 mmHg; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.2 (q, 2H), 3.4 (t, 1H), 1.9 (q, 2H), 1.1-1.5 (m, 13H), 0.9 (t, 3H).

3-Oxooctanenitrile (2)

To 80 mL of CH_2Cl_2 was added *N, O*-dimethyl hydroxylamine (4.3 g, 44 mmol) and hexanoyl chloride (5.4 g, 40 mmol). The reaction mixture was cooled to 0 °C and pyridine (7.0 g, 89 mmol) was slowly added. The mixture was warmed to room temperature and stirred for 1 h. The solvent was then removed and the product was diluted with brine. The solution was extracted with CH_2Cl_2 and then washed with 10% aqueous HCl to remove the excess pyridine. The solution was then dried over $MgSO_4$ and Kugelrohr distilled to provide the Weinreb amide (5.94 g, 37.4 mmol, 93% yield).

To 90 mL of THF at -78 °C was slowly added $(i\text{-Pr})_2NH$ (5.6 g, 55.7 mmol) and *n*-BuLi in hexanes (36 mL of a 1.6 M solution, 58 mmol). The reaction mixture was stirred at -78 °C for 10 min then allowed to warm to room temperature. The mixture was then cooled again to -78 °C and to the reaction was slowly added dry CH_3CN (2.4 g, 57 mmol) in 5 mL of THF. The resulting mixture was stirred at -78 °C for 3 h then warmed to 0 °C and stirred for 1 h. The reaction was then quenched with 1 M HCl (35 mL). The mixture was then diluted with Et_2O, washed with brine, and then extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, then subjected to flash chromatography in 6:1 hexanes/EtOAc. The resulting oil was Kugelrohr distilled to provide the product as a colorless oil (2.97 g, 21.4 mmol, 58% yield): bp 70 °C/0.1 mmHg; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 2H), 2.57 (t, 2H), 1.6 (m, 2H), 1.28 (m, 4H), 0.86 (t, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 197.74, 113.91, 42.18, 31.98, 31.00, 23.03, 22.33, 13.84.

Ethyl 2-Cyano-2-methyl-3-phenylpropionate (3)

An oven dried round bottom flask containing a stir bar was purged with argon. Sodium hydride (60% dispersion in mineral oil, 0.796 g, 19.9 mmol) was added and the flask was again purged with argon. To the NaH was added THF (20 mL), and the suspension was cooled to 0 °C. To the suspension was slowly added ethyl cyanoacetate (6.8 g, 60 mmol) in THF (10 mL). After 15 min benzyl bromide (3.5 g, 20 mmol) was added dropwise via syringe to the solution. The resulting reaction mixture was allowed to stir at 0 °C for 30 min and then allowed to warm to room temperature with stirring for 4.5 h. The mixture was then quenched with H_2O (30 mL) and diluted with Et_2O. The aqueous layer was removed and the organic layer was washed twice with brine. The combined aqueous layers were then extracted three times with Et_2O. The combined organic extracts were then dried over anhydrous $MgSO_4$ and the solvent was removed by rotary evaporation. Final purification involved Kugelrohr distillation which afforded a colorless oil (1.2 g, 30% yield). This oil was added to a sample of the same product made in a separate reaction (total amount of 1.32 g, 6.5 mmol). The combined oils were dissolved in THF (2 mL) and slowly added dropwise via syringe to a suspension of NaH (0.295 g, 7.4 mmol) in THF (4 mL) which had been cooled to 0 °C. The mixture was allowed to stir at 0 °C for 15 min. To the solution was then added iodomethane (1.1 g, 8.0 mmol) and the mixture was allowed to stir for 2.5 h. The mixture was then quenched with 6 mL of H_2O, and diluted with Et_2O. The aqueous layer was separated and the organic layer was washed twice with brine. The aqueous layers were then extracted three times with Et_2O and the combined organic extracts were dried over anhydrous $MgSO_4$. Final purification involved Kugelrohr distillation and yielded a colorless oil (1.0098 g, 71.6% yield): bp 78 °C/0.1 mmHg; R_f = 0.49 (3:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 6.9 Hz, 3H), 1.62 (s, 3H), 3.13 (dd, 2H), 4.19 (q, J = 6.9 Hz, 2H), 7.3 (m, 5H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 169.01, 134.17, 129.98, 128.54, 127.86, 119.73, 62.74, 45.28, 43.61, 23.10, 13.80; IR (neat) 1017.0, 1118.8, 1497.0, 1584.7, 1603.8, 1741.6, 2244.0, 2939.1, 3032.0, 3064.1 cm^{-1}.

Diethyl 2-Cyano-2-n-heptylpentanedioate (4)

To NaH (0.52 g, 13 mmol) was added 9 mL of dry DMF. The slurry was then cooled to 0 °C and 1 (2.71 g, 12.9 mmol) in 4 mL of DMF was slowly added with stirring. The reaction mixture was stirred until H_2 evolution ceased (15 min). Ethyl 3-bromopropionate (3.1 g, 17.2 mmol) was then slowly added. The reaction mixture was heated at 50 °C for 5.5 h, then allowed to cool to room temperature. The reaction was quenched with 15 mL of water, then diluted with Et_2O. The ether layer was washed with brine, and the aqueous layers were extracted with Et_2O. The

combined organic extracts were dried over $MgSO_4$ and concentrated. The product was subjected to flash chromatography in 5% EtOAc/hexanes. The pure fractions were condensed and all remaining traces of solvent were removed *in vacuo* to provide the product as a colorless oil (2.72 g, 8.7 mmol, 68% yield): R_f = 0.49 (3:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.24 (q, J = 7.08 Hz, 2H), 4.10 (q, J = 7.08, Hz, 2H), 1.19-2.61 (m, 22H), 0.84 (m, 3H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 171.60, 168.60, 118.72, 62.77, 60.80, 48.95, 37.30, 31.96, 31.53, 30.19, 29.04, 28.79, 25.23, 22.55, 22.46, 14.05, 13.99, 13.93; IR (neat) 1023.8, 1739.0, 2243.3, 2858.1, 2929.1 cm^{-1}.

Ethyl 2,5-Dicyano-2-n-heptylpentanoate (5)

To NaH (0.436 g, 10.9 mmol) was added 8 mL of dry DMF. The resulting slurry was cooled to 0 °C and 1 (2.27 g, 10.8 mmol) in 3 mL of DMF was slowly added. The reaction mixture was stirred until H_2 evolution ceased (15 min), then 4-chlorobutyronitrile (1.5 g, 14.5 mmol) was slowly added. The reaction was then heated at 70 °C for 3 h. The mixture was then cooled to room temperature and quenched with 15 mL of water. The mixture was diluted with Et_2O and washed with brine. The aqueous layer was extracted three times with Et_2O, and then the combined organic extracts were dried over $MgSO_4$. The extracts were concentrated and then subjected to flash chromatography in 3:1 hexanes / EtOAc. The pure fractions were concentrated, then all traces of solvent were removed *in vacuo* to provide the product as a colorless oil (2.49 g, 9.0 mmol, 83% yield): R_f= 0.24 (3:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.25 (q, J = 7.08 Hz, 2H), 2.39 (t, J = 6.59 Hz, 2H), 1.19-2.10 (m, 19H), 0.83 (m, 3H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 168.46, 118.64, 118.46, 62.82, 49.19, 37.34, 35.69, 31.43, 28.92, 28.67, 25.10, 22.37, 21.40, 16.79, 13.93, 13.86; IR (neat) 1019.9, 1741.1, 2245.9, 2858.1, 2929.7 cm^{-1}.

N,N-Diethyl 4-Cyano-4-ethoxycarbonylundecanamide (6)

To 20 mL of dry CH_2Cl_2 was added 3-chloropropionyl chloride (4.0 g, 31.4 mmol). The solution was cooled to 0 °C and Et_2NH (4.9 g, 68 mmol) was slowly added. The reaction mixture was stirred at 0 °C for 1 h, then warmed to room temperature. The product was washed with aqueous $NaHCO_3$ and with brine. The combined aqueous layers were extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated to provide an oil which was Kugelrohr distilled to afford*N,N*-diethyl-3-chloropropionamide (5.1 g, 31.3 mmol, 99.6% yield).

To NaH (0.475 g, 11.9 mmol) was added 7 mL of dry DMF. The slurry was cooled to 0 °C and 1 (2.51 g, 11.8 mmol) in 3 mL of DMF was slowly added. The reaction mixture was allowed to stir until H_2 evolution ceased (15 min). To the solution was then added *N,N*-diethyl-3-chloropropionamide (2.51 g, 15.4 mmol). The reaction was then heated at 70 °C for 2.5 h, then cooled to room temperature. The reaction was then quenched with saturated ammonium chloride (10 mL) and diluted with Et_2O. The organic extract was washed with brine and the combined aqueous layers were extracted with Et_2O. The combined ether extracts were dried over $MgSO_4$ and concentrated. The product was then subjected to flash chromatography in 3:1 hexanes/EtOAc. The pure fractions were concentrated and excess solvent was removed *in vacuo* to provide the product as an oil (1.07 g, 3.2 mmol, 27%): 2.21 g of impure product were also isolated but not subjected to further purification: R_f = 0.55 (2:1 EtOAc/hexanes); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.23 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.21-3.39 (m, 4H), 2.5 (m, 1H), 2.25 (m, 2H), 2.1 (m, 1H), 1.9 (m, 1H), 1.75 (m, 1H), 1.55 (m, 1H), 1.18-1.33 (m, 12H), 1.13 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H), 0.83 (m, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 169.52, 168.82, 119.10, 62.57, 49.31, 41.74, 40.14, 37.38, 32.47, 31.49, 29.04, 28.85, 28.76, 25.27, 22.43, 14.09, 14.00, 13.91, 12.90; IR (neat) 1018.9, 1071.8, 1650.1, 1738.5, 2242.6, 2858.2, 2930.0 cm^{-1}; LRMS (GC/MS, EI) *m/z* 338, 265, 240, 192, 154, 128, 115, 58.

Ethyl 2-(4-Chloroprop-1-yl)-2-cyanononanoate (7)

To NaH (0.537 g, 13.4 mmol) was added 10 mL of dry DMF. The slurry was cooled to 0 °C and 1 (2.8 g, 13.3 mmol) in 4 mL of DMF was slowly added. The reaction mixture was stirred until H_2 evolution ceased (15 min), then 1,4-dichlorobutane (3.5 g, 27.4 mmol) was added and the reaction was heated to 60 °C for 5 h. The reaction was then cooled to room temperature and quenched with saturated aqueous ammonium chloride (15 mL). The resulting mixture was diluted with Et_2O and washed with brine. The combined aqueous layers were extracted with Et_2O, and the combined organic extracts were then dried over $MgSO_4$. The product was concentrated, then subjected to flash chromatography in 2% EtOAc/hexanes. The pure fractions were concentrated to provide an oil which was Kugelrohr distilled to afford the product as a colorless oil (2.55 g, 8.5 mmol, 64%): bp 110 °C/0.1 mmHg; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.24 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.49 (t, J = 6.3 Hz, 2H CH_2Cl), 1.18-1.87 (m, 21H), 0.83 (m, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 169.03, 119.20, 62.56, 49.70, 44.05, 37.39, 36.49, 31.90, 31.50, 29.03, 28.74, 25.22, 22.71, 22.42, 13.98, 13.90; IR (neat) 1021.5, 1096.1, 1740.5, 2243.1, 2857.3, 2926.2 cm^{-1}.

Ethyl 2-Methyl-3-phenylpropionate (8). General procedure for the Samarium(II) Iodide reduction of α-Cyano esters

Samarium metal (0.5064 g, 3.368 mmol) was added to an oven dried round bottom flask containing a stir bar under

argon. The flask was again purged with argon. To the samarium was added THF (23 mL) followed by CH_2I_2 (0.811 g, 3.031 mmol). The resulting blue solution was stirred vigorously at room temperature for 2.5 h. To this blue solution of SmI_2 was added HMPA (2.8 mL, 16.094 mmol) via syringe and the resulting purple solution was allowed to stir at room temperature for 20 min. The solution was then cooled to 0 °C and to the solution was added 3 (0.2204 g, 1.0156 mmol) and methanol (0.082 mL, 2.031 mmol) in THF (20 mL) over a 20 min period. The resulting purple solution was stirred at 0 °C until TLC analysis showed the reaction was complete. The reaction was then quenched with saturated aqueous $NaHCO_3$ (35 mL). The mixture was then diluted with Et_2O and the aqueous phase was separated. The organic layer was washed twice with saturated aqueous $NaHCO_3$ and once with brine. The organic layer was separated and the combined aqueous layers were extracted three times with Et_2O. The combined organic extracts were then dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation and the product was purified by flash chromatography in 25% EtOAc/hexanes, and then Kugelrohr distilled under high vacuum, giving a clear oil (0.1561 g, 0.81 mmol, 80% yield): bp 56 °C/0.1 mmHg; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.13-7.29 (m, 5H), 4.07 (q, J = 7.2 Hz, 2H), 3.00 (m, 1H), 2.60-2.74 (m, 2H), 1.10-1.20 (m, 6H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 176.18, 139.45, 129.02, 128.33, 126.29, 60.30, 41.52, 39.76, 16.82, 14.19; IR (neat) 1029.3, 1043.2, 1063.1, 1095.0, 1117.2, 1495.7, 1604.3, 1731.9, 2936.2, 2977.9, 3028.4, 3063.4, cm^{-1}; HRMS calcd for $C_{12}H_{16}O_2$: 192.1150, found 192.1149; LRMS (GC/MS, EI) *m/z* 192, 147, 118, 107, 91, 65, 39.

Ethyl 4-Ethoxycarbonylundecanoate (9)

Using the general procedure (with ethanol as the proton source), 4 (0.4273 g, 1.37 mmol) was reduced to provide 0.2963 g (1.04 mmol, 75% yield) of the title compound: bp 92 °C/0.1 mmHg; R_f = 0.62 (3:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.10 (m, 4H), 2.25 (m, 3H), 1.1-1.95 (m, 20H), 0.84 (m, 3H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 175.77, 173.14, 60.33, 60.18, 44.78, 32.26, 32.01, 31.71, 29.38, 29.04, 27.14, 22.55, 14.24, 14.14, 14.05, 14.00; IR (neat) 1031.4, 1096.3, 1736.1, 2856.6, 2928.9 cm^{-1}; HRMS calcd for $C_{16}H_{31}O_4$ $(M+H)^+$: 287.2222, found 287.2213; LRMS (GC/MS, EI) *m/z* 241, 198, 188, 142, 124, 114, 69, 55.

Ethyl 2-(3-Cyanoprop-1-yl)nonanoate (10)

Using the general procedure (with ethanol used as the proton source), 5 (0.3508 g, 1.26 mmol) was reduced to provide 0.2709 g (1.07 mmol, 85% yield) of the title compound: bp 100 °C/0.1 mmHg; R_f = 0.30 (3:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.12 (q, J = 7.08 Hz, 2H), 2.32 (m, 3H), 1.18-1.80 (m, 19H), 0.84 (m, 3H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 175.62, 119.36, 60.29, 44.87, 32.36, 31.69, 31.10, 29.35, 29.02, 27.16, 23.29, 22.54, 17.04, 14.24, 14.00; IR (neat) 1025.6, 1732.1, 2246.1, 2856.8, 2928.1 cm^{-1}; HRMS calcd for $C_{15}H_{28}NO_2$ $(M+H)^+$: 254.2120, found 254.2108; LRMS (GC/MS, EI) *m/z* 208, 180, 155, 122, 109, 83, 41.

N,N,-Diethyl 4-Ethoxycarbonylundecanamide (11)

Using the general procedure (with ethanol as the proton source), 6 (0.3924 g, 1.16 mmol) was reduced to provide 0.3819 g (1.02 mmol, 88% yield) of the title compound: bp 126 °C/0.1 mmHg; R_f = 0.51 (2:1EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.10 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.17-3.41 (m, 4H), 2.14-2.39 (m, 3H), 1.78-1.89 (m, 2H), 1.11-1.64 (m, 21H), 0.83 (m, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 176.13, 171.39, 60.04, 45.14, 41.79, 40.03, 32.48, 31.68, 30.68, 29.39, 29.01, 27.69, 27.18, 22.53, 14.24, 14.20, 13.98, 12.99; IR (neat) 1042.4, 1070.9, 1096.4, 1646.7, 1730.6, 2856.6, 2929.6, 2958.0 cm^{-1}; HRMS calcd for $C_{18}H_{35}NO_3$: 313.2617, found 313.2620; LRMS (GC/MS, EI) *m/z* 313, 268, 228, 182, 149, 115, 100, 72.

Ethyl 6-Chloro-2-(hept-1-yl)hexanoate (12)

Using the general procedure (with ethanol as the proton source), 7 (0.4133 g, 1.37 mmol) was reduced to provide 0.2314 g (0.84 mmol, 61% yield) of the title compound: bp 80 °C/0.1 mmHg; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.11 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.49 (t, J = 6.6 Hz, 2H, CH_2Cl), 2.29 (m, 1H), 1.18-1.88 (m, 21H), 0.85 (m, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 176.29, 60.04, 45.51, 44.73, 32.42, 31.72, 31.59, 29.42, 29.07, 27.30, 24.70, 22.56, 14.27, 14.00; IR (neat) 1030.2, 1095.9, 1731.8, 2856.2, 2927.1 cm^{-1}; HRMS calcd for $C_{15}H_{29}ClO_2$: 276.1856, found 276.1847; LRMS (GC/MS, EI) *m/z* 276, 231, 191, 186, 143, 101, 73, 41.

3-Oxo-2,2-bis(2-propenyl)octanenitrile (13)

To dry EtOH (13 mL) was slowly added NaH (0.181 g, 4.5 mmol), followed by 2 (0.283 g, 2 mmol) in EtOH (2 mL). The solution was stirred for 30 min, then allyl bromide (0.62 g, 5.1 mmol) was slowly added. The reaction was stirred overnight, then quenched with 10 mL of water and diluted with Et_2O. The organic layer was washed with brine, then the combined aqueous layers were extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was subjected to flash chromatography using 4% EtOAc/hexanes. The pure fractions were concentrated and all remaining traces of solvent were removed *in vacuo*, affording the product as a colorless oil (0.225 g, 1 mmol, 51% yield). Also isolated was 40 mg of slightly impure product. Start-

ing material and monoalkylated product were visible by TLC: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.75 (m, 2H), 5.15 (m, 4H), 2.65 (t, 2H), 2.55 (dd, 2H), 2.40 (dd, 2H), 1.55 (p, 2H), 1.25 (m, 4H), 0.85 (t, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 203.99, 130.52, 121.00, 120.02, 53.67, 42.14, 40.34, 30.91, 22.55, 22.30, 13.79; IR (neat) 3082.6, 2957.3, 2871.9, 2235.9, 1725.8, 1441.3, 1400.2 cm^{-1}.

3-Oxo-2-(2-propenyl)octanenitrile (14)

Using the general procedure, 13 (0.104 g, 0.47 mmol) was reduced to provide 0.0407 g (0.23 mmol, 48% yield) of the title compound: bp 74 °C/0.1 mmHg; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.68-5.83 (m, 1H), 5.14-5.26 (m, 2H), 3.43 (m, 1H), 2.49-2.74 (m, 4H), 1.59 (p, 2H), 1.20-1.36 (m, 4H), 0.86 (t, 3H). ^{13}C-NMR (400 MHz, $CDCl_3$) δ 200.38, 131.67, 119.76, 117.12, 43.58, 41.35, 32.85, 30.95, 22.87, 22.28, 13.78; LRMS (GC/MS, EI) *m/z* 179, 150, 136, 108, 99, 71, 43.

1-(2-Propen-1-yl)-2-oxocycloheptanecarbonitrile (15)

To 6.4 mL of dry Et_2O was added MeMgBr (14.6 mL of a 3 M Et_2O solution, 43.80 mmol). The solution was cooled to 0 °C and *N*-methylaniline (4.7 g, 44.3 mmol) in 17.5 mL of dry benzene was slowly added dropwise (the addition took 45 min). The solution was then heated to reflux and then 1,6-dicyanohexane (4.0 g, 29.4 mmol) in 44 mL of 1:1 Et_2O/benzene was slowly added dropwise (the addition took 2 h). The reaction mixture was stirred at reflux temperature overnight, then cooled to room temperature and quenched with 100 mL of 15% aqueous HCl (exothermic). This mixture was stirred for 15 min, then saturated with NaCl and repeatedly extracted with EtOAc. The product was dried over $MgSO_4$, then subjected to flash chromatography in 3:1 hexanes/EtOAc. The resulting oil was Kugelrohr distilled to provide 2-oxocycloheptanecarbonitrile as a colorless oil (1.61 g, 11.8 mmol, 40% yield): mixture was diluted with Et_2O and washed with brine. The combined aqueous layers were then extracted with Et_2O, and the organic extracts were then dried over $MgSO_4$. The product was concentrated and subjected to flash chromatography in 30% EtOAc/hexanes. The pure fractions were concentrated, then Kugelrohr distilled to provide the product as a colorless oil (1.21 g, 6.8 mmol, 65%): bp 68 °C/0.1 mmHg; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.65-5.80 (m, 1H), 5.20 (m, 2H), 1.10-2.75 (m, 12H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 204.93, 130.72, 120.71, 119.80, 54.53, 40.78, 40.71, 35.02, 28.55, 25.68, 24.31; IR (neat) 3081.6, 3009.9, 2934.8, 2859.2, 2240.2, 1713.0, 1455.9, 1444.5, 1417.7 cm^{-1}.

2-Oxocycloheptanecarbonitrile (16)

Using the general procedure (with EtOH as a proton source), 15 (0.1296 g, 0.73 mmol) was reduced to provide 0.0680 g (0.50 mmol, 68% yield) of the title compound: bp 70 °C/0.1 mmHg; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.68 (m, 1H), 2.60 (t, 2H), 1.5-2.2 (m, 8H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 2.03.37, 117.42, 44.66, 42.23, 29.07, 28.66, 27.68, 23.26.

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