of PtO_2 and 5 drops of concentrated HCl. Hydrogenation was carried out under 1 atm of pressure of hydrogen for 5 h. The solution was filtered through Celite and the solvent removed in vacuo to leave a colorless oil. Crystallization from methanol–ether gave 30 mg of the hydrochloride salt of **14a**: mp 166–168 ° C; NMR and IR identical with those of **14a** obtained from aldehyde–amide **11a**.

Acknowledgments. This investigation was supported by grants from the National Cancer Institute (CA-12059) and the American Cancer Society (CI-102K). We thank the National Science Foundation for a grant which assisted in the purchase of a FT NMR spectrometer.

Registry No.—**1c**, 36455-21-7; **2a**, 2107-70-2; **2c**, 36418-96-9; **2e**, 1135-15-5; **3c**, 20872-69-9; **3d**, 65899-35-6; **4a**, 20944-14-3; **4b**, 30034-51-6; **4c**, 65899-36-7; **4d** HCl, 65899-37-8; **4e**, 65899-38-9; **5a**, 65899-28-7; **5a** HCl, 32487-02-8; **5c**, 65899-29-8; **5c** HCl, 65899-19-6; **5d**, 65899-30-1; **5d** HCl, 65899-20-9; **5e**, 65899-31-2; **5e** HCl, 65899-21-0; **6a** perchlorate, 65899-22-1; **6h**, 65899-23-2; **9a** HCl, 61660-06-8; **9b**, 61660-05-7; **10** isomer I, 51744-25-3; **10** isomer II, 30040-57-4; **14a** HCl, 65899-24-3; **14b**, 58141-98-3; **14c**, 65899-25-4; **22**, 65899-26-5; **23**, 65899-27-6.

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Utilization of β,γ-Unsaturated Aldehyde Equivalents in the Synthesis of Substituted 2-Halonicotinic Acid Derivatives

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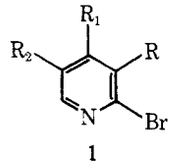
A convenient synthetic method is described for the preparation of 4- and/or 5-substituted 2-halonicotinic acid derivatives. The condensation of alkylidenemalononitriles or alkylidenecyanoacetates with either $HC(OEt)_3$ or DMF acetal yields the equivalent of a β,γ-unsaturated aldehyde which undergoes cyclization with acid to provide polysubstituted pyridines. However, the general utility of the reaction between DMF acetal and alkylidenemalononitriles is severely limited by the formation of dimeric type derivatives, **31–34**. This complication is overcome by the acid-catalyzed reaction of $HC(OEt)_3$ with alkylidenemalononitriles. Conversion of substituted ethyl nicotinates derived from alkylidenecyanoacetates to the corresponding trifluoromethyl derivatives is also described. Reaction of the unsymmetrical olefin 1-methylpropylidenemalononitrile with DMF acetal and with $HC(OEt)_3$ yields, in a regiospecific manner, two different β,γ-unsaturated aldehyde equivalents, which after acid cyclization afford 4-ethyl- and 4,5-dimethyl-2-bromonicotinonitriles, respectively.

An interest in derivatives of 2-halonicotinic acid of the type **1** led to a search for a synthetic method capable of generating such systems. Although several syntheses of the parent, ethyl 2-halonicotinate, and certain substituted derivatives have been described,[1,2] none of these have been extended to provide a versatile method for the introduction of alkyl or aryl groups into the 4 and/or 5 positions.[3]



1

R = CO_2Et, CN, or CF_3
R_1,R_2 = alkyl, aryl, or H

One of the most general of these reported methods involves the Knoevenagel condensation of 1,3-dicarbonyl compounds (**2**) (or their chemical equivalents) with α-cyanoacetamide (**3**). This condensation is accompanied by cyclization, yielding 2-pyridones of the type **4** which are convertible by standard methods[4] to 2-halopyridines (Scheme I). Although a number of 6-substituted and 4,6-disubstituted 2-hydroxynicotinic acid derivatives have been prepared by this procedure, the method

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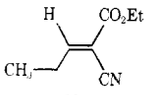
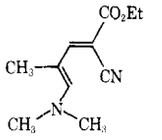
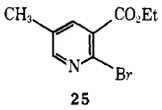
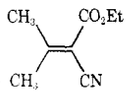
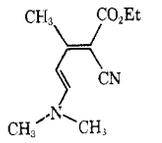
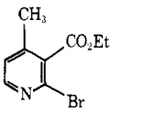
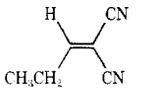
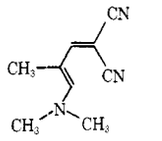
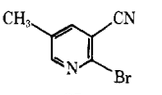
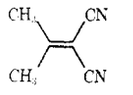
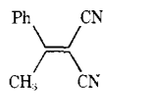
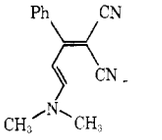
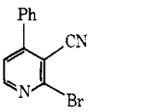
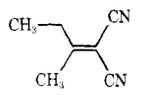
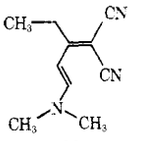
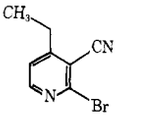
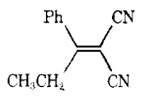
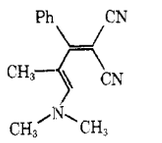
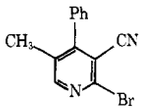
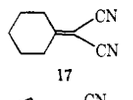
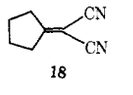
Table I. Nicotinic Acid Derivatives Via DMF Acetal Route (Method A)[a]

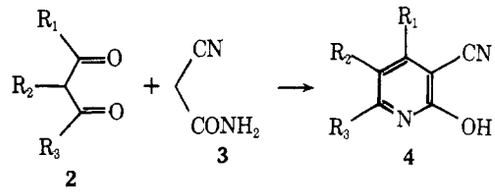
Knoevenagel product	β,γ-Unsaturated aldehyde equivalent	Nicotinic acid derivative	Overall yield, %
 10	 19	 25	35
 11	 20	 26	58
 12	 21	 27	5
 13	Not obtained		
 14	 22	 28	22
 15	 23	 29	16
 16	 24	 30	3
 17	Not obtained		
 18	Not obtained		

[a] Registry no.: **10**, 56569-41-6; **11**, 759-58-0; **12**, 52833-34-8; **14**, 5447-87-0; **15**, 13017-50-0; **16**, 10432-39-0; **19**, 65996-10-3; **20**, 65996-11-4; **21**, 65996-12-5; **22**, 65996-13-6; **23**, 65996-14-7; **24**, 65996-15-8; **25**, 65996-16-9; **26**, 65996-17-0; **27**, 65996-18-1; **28**, 65996-19-2; **29**, 65996-20-5; **30**, 65996-21-6.

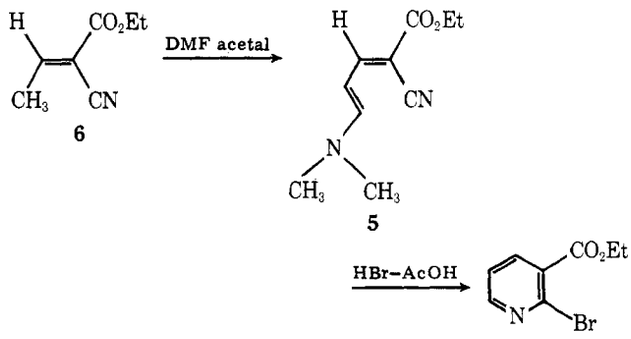
is not amenable to the synthesis of the corresponding 4- and/or 5-substituted compounds. In the case of 5-substituted derivatives,[5,6] this limitation is due to the lack of a convenient synthesis for 2-substituted malonaldehydes. The only example of a 4-substituted 2-hydroxynicotinic acid derivative has been reported by Powers and Ponticello,[7] but the synthesis suffers from low yields and a lack of general applicability.

Another approach to ethyl 2-halonicotinate has been reported by Bryson et al.[8] and involves the intramolecular cyclization of ethyl 5-(*N,N*-dimethylamino)-2-cyano-2,4-pentadienoate (**5**), obtainable by the base-catalyzed[8c] reaction of *N,N*-dimethylformamide dimethyl acetal (DMF acetal) with

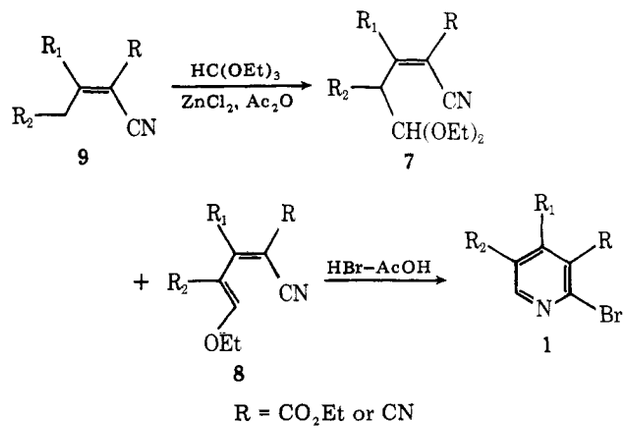
Scheme I



Scheme II



Scheme III



R = CO_2Et or CN

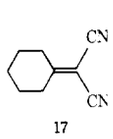
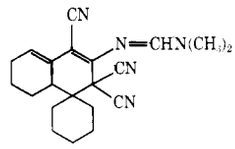
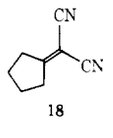
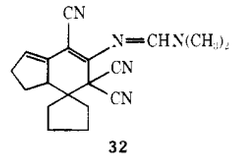
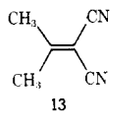
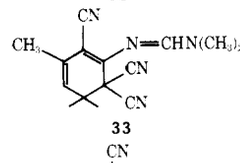
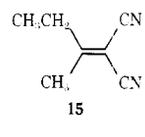
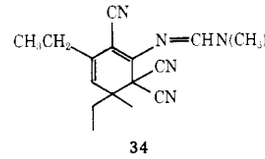
olefin **6**, as illustrated in Scheme II. In this paper, we wish to report on the extension of this method to the synthesis of substituted pyridines of the type **1** and on the utilization of β,γ-unsaturated acetals **7** and enol ethers **8** obtained from the acid-catalyzed reaction of triethyl orthoformate with vinylogous active methylene compounds **9** (Scheme III).

Results and Discussion

Our initial studies involved the reaction of olefins **10–18** with DMF acetal (method A, Table I). These olefins, in turn, were prepared by Knoevenagel condensation[9] of the apppropriate aldehyde or ketone with ethyl α-cyanoacetate or malononitrile. For the alkylidenecyanoacetates **10** and **11**, the reaction yielded the β,γ-unsaturated aldehyde equivalents **19** and **20**, which were converted directly by acid cyclization (HBr–AcOH) to **25** and **26** in yields of 35 and 58%, respectively. In the case of the alkylidenemalononitriles **12–18**, the reaction gave variable results. The yield of 2-bromo-4-phenylnicotinonitrile (**28**) from **14** was 22%; this represents a significant improvement over the previously reported[7] yield of 5% for 3-cyano-4-phenyl-2-pyridone. Overall, the nicotinonitriles **27–30** were obtained in low yield. Three substrates, **13**, **17**, and **18**, failed to yield the intermediate dienes on reaction with DMF acetal.

As summarized in Table II, the reaction of DMF acetal with **13**, **15**, **17**, and **18** gave the complex formamidines **31–34** as the

Table II. Dimers[a]

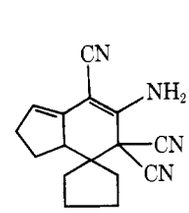
Olefin	Product	NMR, δ	Mass spectra
 17	 31	7.82 (1 H, s), 6.3 (1 H, m), 3.15 (6 H, d), 3.0–1.2 (17 H, m)	Calcd for $C_{21}H_{25}N_5$: 347.2096 Found: 347.2110
 18	 32	7.9 (1 H, s), 5.95 (1 H, q), 3.15 (6 H, d), 2.9–1.3 (13 H, m)	Calcd for $C_{19}H_{21}N_5$: 319.1797 Found: 319.1796
 13	 33	8.1 (1 H, s), 5.25 (1 H, q), 3.15 (6 H, d), 1.95 (3 H, d), 1.35 (6 H, s)	Calcd for $C_{15}H_{17}N_5$: 267.1484 Found: 267.1486
 15	 34	8.0 (1 H, s), 5.25 (1 H, bs), 3.15 (6 H, d), 2.8–0.8 (13 H, m)	Calcd for $C_{17}H_{21}N_5$: 295.1797 Found: 295.1790

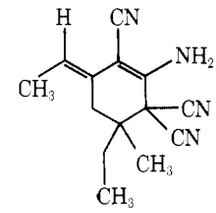
[a] Registry no.: **13**, 13166-10-4; **17**, 354-73-8; **18**, 5660-83-3; **31**, 65996-22-7; **32**, 65996-23-8; **33**, 65996-24-9; **34**, 66017-99-0.

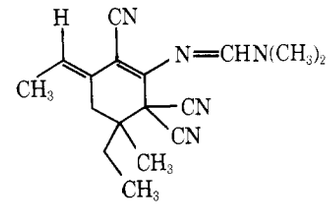
sole or major product. The structural assignment of these compounds was based on their proton NMR and high-resolution mass spectra. Integration of the olefinic signal relative to the formamidine proton revealed a 1:1 ratio, thereby confirming the relative positions of the double bonds in structures **31–33.** The structure of **34** is clearly supported by the appearance of the olefinic proton as a weakly coupled triplet at δ 5.25 (J = 0.5 Hz) rather than as a quartet which would be expected for the alternative exo possibility (**38**).

Since alkylidenemalononitriles are known to dimerize under base catalysis,[10–13] it was postulated that **31–34** resulted from the reaction of the intermediate dimers with DMF acetal. To test this hypothesis, cyclohexylidenemalononitrile (**17**) was treated (neat) with a catalytic amount of piperidine, according to the method of Weir and Hyne,[11,12] to yield the dimer **35.** Subsequent treatment of **35** with DMF acetal afforded the formamidine **31,** which was identical in all respects (IR and NMR spectra and mixed melting point) with the product formed directly from the reaction of **17** with DMF acetal. (Scheme IV).

Similarly, transformation of cyclopentylidenemalononitrile (**18**) with piperidine yielded dimer **36,** which was converted to **32** in an analogous manner. The dimeric product formed on treating **15** with base, according to the method of Weir and Hyne,[12] was assigned structure **37** based on NMR spectroscopy and is in agreement with the previously reported structure. Treatment of **37** with DMF acetal gave formamidine **38,**


36


37


38

which was not identical with formamidine **34** obtained on reaction of **15** with DMF acetal.

Thus, this last example tends to argue against the formation of the formamidine from the intermediate dimer. Therefore, the exact mechanism for the formation of these formamidine dimeric products **31–34** must be left undefined.

The thermodynamic products **31–33** were obtained in all cases, except for **34,** where the product of kinetic control was isolated. Refluxing **34** in xylene resulted in almost complete conversion of kinetic product **34** to the thermodynamic product **38** (~80%), while compounds **31–33** remained unchanged under the same conditions.

It was found that the use of alkylidenecyanoacetates in place of the malononitriles obviates the problems encountered in the DMF acetal reaction. Thus, the cyanoesters are the substrate of choice for entry into the desired 2-halonicotinate system; this is best illustrated in examples **25** and **26.**

In addition, **25** and **26** were hydrolyzed with 10% NaOH solution to the corresponding acids **39** and **40** in high yield (Scheme V). Reaction of these acids with SF_4–HF gave the trifluoromethylpyridines **41** and **42.**[14] In the NMR spectrum

Scheme IV

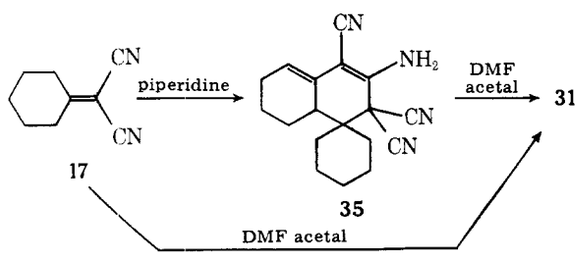
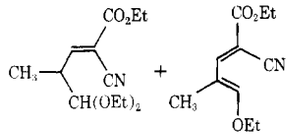
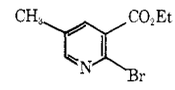
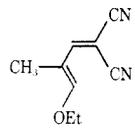
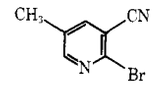
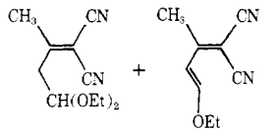
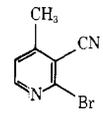
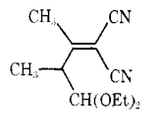
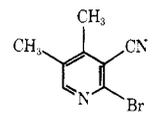
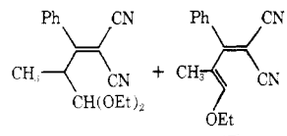
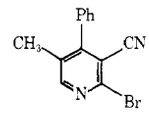
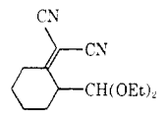
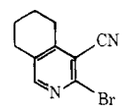
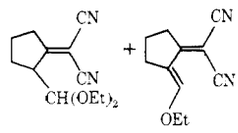
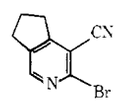


Table III. Nicotinic Acid Derivatives Via $HC(OEt)_3$ Route (Method B)[a]

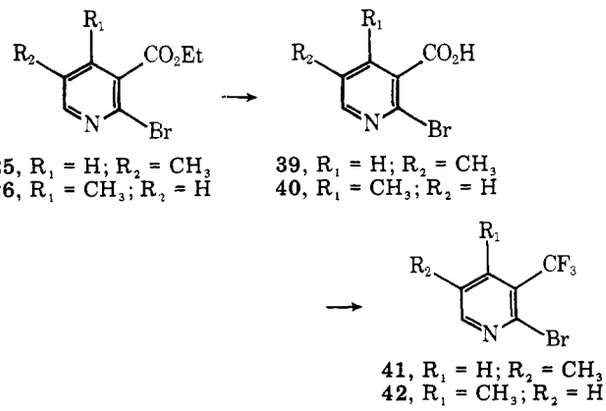
Knoevenagel product	β,γ-Unsaturated aldehyde equivalent	Yield, %	Nicotinic acid derivative	Overall yield, %
10	 **43a** + **43b**	74	 **25**	40
12	 **44**	67	 **27**	15
13	 **45a** **45b**	*b*	 **50**	23
15	 **46**	70	 **51**	29
16	 **47a** **47b**	95	 **30**	42
17	 **48**	29	 **52**	15
18	 **49a** **49b**	36	 **53**	15

[a] Registry no.: **43a**, 65995-91-7; **43b**, 65995-92-8; **44**, 65995-93-9; **45a**, 65995-94-0; **45b**, 65995-95-1; **46**, 65995-96-2; **47a**, 65995-97-3; **47b**, 65995-98-4; **48**, 65995-91-5; **49a**, 65996-00-1; **49b**, 65996-01-2; **50**, 65996-02-3; **51**, 65996-03-4; **52**, 66017-97-8; **53**, 66996-04-5. [b] See footnote *b* in Table V.

of **42**, the C-4 methyl group was characteristically coupled to the adjacent trifluoromethyl moiety as a quartet with $J = 3$ Hz.

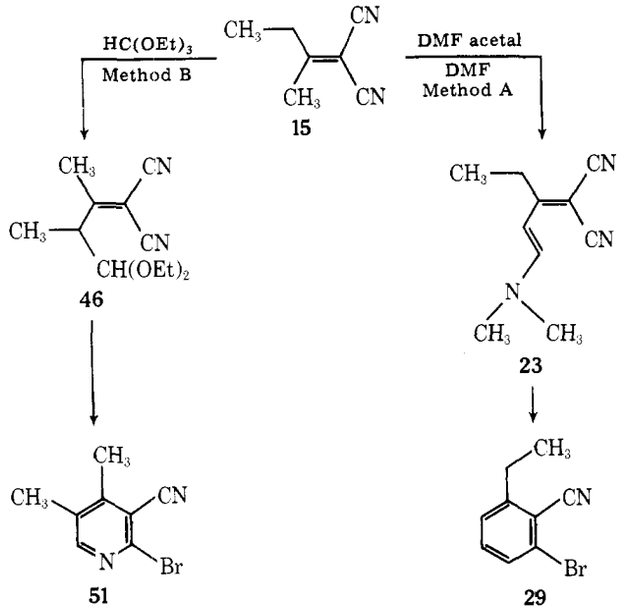
The difficulties encountered in the preparation of haloni-cotinonitriles from certain alkylidenemalononitriles (**13**, **17**, and **18**) using DMF acetal prompted a search for an alternate way to generate the β,γ-unsaturated aldehyde equivalents. As outlined in Scheme III, the limitations inherent in the Bryson method were overcome by the synthesis and utilization of the β,γ-unsaturated acetals **7** and enol ethers **8**. Although the reaction of triethyl orthoformate with diethyl malonate to afford ethyl ethoxymethylenemalonate has been reported,[15] its reaction with vinylogous active methylene compounds to generate the β,γ-unsaturated aldehyde derivatives **7** and **8** has not been described.

Scheme V



The general versatility and utility of this conversion are illustrated by the examples presented in Table III. Reaction of these olefins, prepared by the Knoevenagel condensation, with $HC(OEt)_3$ (method B) yielded the corresponding β,γ-unsaturated acetals as the major products; in the case of propylidenemalononitrile (**12**), only the β,γ-unsaturated enol ether **44** was isolated. In the reaction of dialkyl olefins **13**, **15**, **17**, and **18**, the ratio of olefin to $HC(OEt)_3$ to Ac_2O was 1:1:2. For condensations where only one alkyl group was available for reaction, as in olefins **10**, **12**, and **16**, the same ratio of reactants was used; however, after refluxing overnight, the volatiles were distilled off, additional reagents ($HC(OEt)_3$–

Scheme VI



Ac_2O) were added, and the reaction mixture was heated at 150 °C for an additional 3 h. In most cases, the unsaturated acetals **43–49** were purified by distillation and their structures determined by proton NMR spectroscopy. All of the acetals exhibited a doublet in the region of δ 4.5 for the $-CH(OEt)_2$ proton, except for **45** where the expected triplet appeared at δ 4.7. In the NMR spectra of compounds **43, 45, 47,** and **49,** the presence of the corresponding enol ethers was also indicated.

Inspection of Tables I and III reveals that the yields of nicotinic acid derivatives are generally higher using the $HC(OEt)_3$ method. As an illustration, compounds **27** and **30** were prepared by both procedures; the overall yields were 5 and 3% using DMF acetal and 15 and 42%, respectively, using the $HC(OEt)_3$ method. For alkylidenemalononitriles **13, 17,** and **18** the DMF acetal method failed to yield β,γ-unsaturated aldehyde equivalents, while the sequence utilizing the acid-catalyzed $HC(OEt)_3$ method proved successful. Thus, the base-catalyzed dimerization reaction is a severe synthetic limitation on the possible extension of the enamine diene system. This difficulty is entirely overcome by the $HC(OEt)_3$ method, thereby making the β,γ-unsaturated acetals much more versatile synthons. Of special note is the utilization of this method and the failure of the DMF acetal procedure for the synthesis of the novel tetrahydroisoquinoline **52** and 4,5-cyclopentenopyridine **53** (see Table III).

As illustrated in Scheme VI, 1-methylpropylidenemalononitrile (**15**) afforded 2-bromo-4-ethylnicotinonitrile (**29**) by the DMF acetal method and 2-bromo-4,5-dimethylnicotinonitrile (**51**) by the $HC(OEt)_3$ procedure. The methylene carbon atom of the ethyl group in **15** reacted with $HC(OEt)_3$ under acid catalysis to yield the β,γ-unsaturated acetal **46,** while the methyl group of **15** reacted with DMF acetal under base catalysis to afford the enamine diene **23.** This result is in accord with the observation that methyl ethyl ketone undergoes reaction on the methyl group in base and on the methylene carbon in acid.[16] Thus, the availability of methods A and B permits a regioselective synthesis of **29** and **51** from the same precursor (**15**).

Although the overall yields of these nicotinic acid derivatives are moderate, no effort was made to optimize the reaction conditions. With the ease of reaction and the ready availability of starting materials, the $HC(OEt)_3$ method offers a relatively simple synthesis of substituted pyridines of type **1.** In addition, the Bryson procedure involving the reaction of DMF acetal with Knoevenagel products has been extended and its utilization in the synthesis of mono- and disubstituted 2-halonicotinic acid derivatives established.

Experimental Section

Infrared spectra were obtained on Perkin-Elmer Model 137 and 257 spectrophotometers. NMR spectra were determined in the indicated solvent on a Varian T-60 spectrometer using tetramethylsilane as an internal standard for proton spectra and fluorotrichloromethane for ^{19}F spectra. Splitting patterns are designated as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; p, pentet; and m, multiplet. Mass spectra were taken on an AEI MS-902 high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 500 mA. The samples were processed by a DS50 data acquisition system. The low-resolution spectra were run at an ionizing voltage of 70 eV and an ionizing current of 100 mA. Melting points were determined on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Liquids were distilled by short-path distillation through a Vigreux column, and boiling points are uncorrected. Silica gel 60 (E. Merck, Darmstadt) was used for column chromatography. Concentration of solutions was accomplished using a Büchi rotary evaporator under water aspirator pressure (20 mm).

Preparation of 1-Propylidenemalononitrile (12). Using the general procedure of Prout,[17] a solution of malononitrile (50 g, 0.76 mol), propionaldehyde (47 g, 0.81 mol), AcOH (10 mL), benzene (140 mL), and alanine (0.5 g) was refluxed for 1.5 h with removal of H_2O in a Dean–Stark trap. After cooling, the solution was poured into H_2O and separated. The aqueous layer was washed with benzene (2 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was distilled to yield 61.7 g (77%) of **12:** bp 45 °C (0.6 mm); ^1H NMR ($CDCl_3$) δ 1.2 (3 H, t), 2.55 (2 H, q), and 7.35 (1 H, t).

The following olefins were prepared by literature procedures: ethyl propylidenecyanoacetate (**10**),[18] ethyl isopropylidenecyanoacetate (**11**),[18] isopropylidenemalononitrile (**13**),[9] 1-phenylethylidenemalononitrile (**14**),[19] 1-methylpropylidenemalononitrile (**15**),[20] 1-phenylpropylidenemalononitrile (**16**),[20,21] cyclohexylidenemalononitrile (**17**),[9] and cyclopentylidenemalononitrile (**18**).[22]

General Procedure for the Preparation of Butadienamines 19–24 Using DMF Acetal (Method A). The preparation of ethyl 2-cyano-5-(*N,N*-dimethylamino)-4-methyl-2,4-pentadienoate (**19**) is presented as an example; details for the synthesis of compounds **20–24** are presented in Table IV.

DMF acetal (8.9 g, 0.75 mol) was added dropwise to a solution of **10** (11.4 g, 0.074 mol) in absolute EtOH (75 mL). After the addition, the solution was heated at reflux for 6 h and then concentrated to dryness to yield 16.9 g of crude **19:** ^1H NMR ($CDCl_3$) δ 1.4 (3 H, t), 2.35 (3 H, s), 3.25 (6 H, s), 4.3 (2 H, q), 6.85 (1 H, s), and 7.6 (3 H, t). This material was used in the next step without further purification.

General Procedure for the Preparation of β,γ-Unsaturated Aldehyde Equivalents 43–49 Using $HC(OEt)_3$ (Method B). The preparation of 1,1-dicyano-4-ethoxy-3-methyl-1,3-butadiene (**44**) is presented as an example; details for the synthesis of compounds **43** and **45–49** are presented in Table V.

A mixture of **12** (11.3 g, 0.104 mol), Ac_2O (21 mL), $HC(OEt)_3$ (16.3 g, 0.11 mol), and $ZnCl_2$ (100 mg) was heated overnight at 145 °C. After 18 h, the volatiles were removed by distillation at atmospheric pressure, Ac_2O (5 mL) and $HC(OEt)_3$ (4 mL) were added, and the mixture was heated at 150 °C. After 10 h, the solution was cooled and added to saturated Na_2CO_3 solution. The aqueous solution was extracted with $CHCl_3$ (3 × 100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was distilled at 138–158 °C (0.3 mm) to give 11.2 g of **44** (67%): ^1H NMR δ 1.4 (3 H, t), 2.05 (3 H, s), 4.15 (2 H, q), 7.0 (1 H, bs), and 7.05 (1 H, s). This material was used in the next step without further purification.

General Procedure for the Preparation of Nicotinic Acid Derivatives Using HBr–AcOH. The preparation of ethyl 2-bromo-5-methylnicotinate (**25**) is presented as an example; details for the synthesis of compounds **26–30** and **50–53** are outlined in Table VI.

Compound **19** (16.9 g) was dissolved in AcOH (50 mL) and the mixture heated at 40 °C. A solution of 30% HBr–AcOH (100 mL) was added dropwise, and then the mixture was heated to 55 °C with stirring. After heating for 0.75 h, the solution was poured onto ice, neutralized with solid Na_2CO_3, and extracted with CH_2Cl_2 (4 × 200 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was distilled at 114–120 °C (0.4 mm) to yield 6.3 g (35%) of **25:** ^1H NMR ($CDCl_3$) δ 1.4 (3 H, t), 2.35 (3 H, s), 4.35 (2 H, q), 7.83 (1 H, d), and 8.23 (1 H, d); MS *m/e* (M^+) 243

Table IV. Experimental Details for DMF Acetal Reaction (Method A)

Olefin (g; mol)	DMF acetal, g (mol)	Solvent (mL)	Temp, °C	Diene (g)	^{1}H NMR, δ
11 (5.7; 0.37)	4.43 (0.037)	Absolute EtOH (50)	25	**20** (7.4)	*a*
12 (8.0; 0.075)	9.0 (0.076)	DMF[b] (30)	25	**21** (8.8)	*a*
14 (10.3; 0.061)	7.61 (0.064)	DMF[b] (14)	0[c]	**22** (13.53)	3.0 (6 H, d), 5.8 (1 H, d), 6.8 (1 H, d), 7.4 (5 H, m)
15 (12.0; 0.1)	12.0 (0.1)	DMF[b] (50)	0[c]	**23** (5.4)[d]	1.05 (3 H, t), 2.6 (2 H, q), 3.15 (6 H, d), 5.5 (1 H, d), 7.3 (1 H, d)
16 (9.0; 0.05)	6.5 (0.055)	DMF[b] (3)	0[c]	**24** (1.3)[d]	2.25 (3 H, s), 3.1 (6 H, s), 6.6 (1 H, s), 7.2 (5 H, m)

[a] NMR spectrum of crude material was too complicated to assign proton resonances. [b] When DMF was used as solvent, the reaction mixture was poured into H_2O, extracted with ether, and backwashed with H_2O. The ether layer was dried, filtered, concentrated to dryness, and used directly in the next step. [c] After the addition of DMF acetal at 0 °C, the reaction mixture was stirred overnight at room temperature. [d] The compound was purified by chromatography on silica gel on elution with $CHCl_3$.

Table V. Experimental Details for HC(OEt)$_3$ Reaction (Method B)

Olefin (g; mol)	$HC(OEt)_3$, g (mol)	Ac_2O, mL	Recovered olefin (g)	β,γ-Unsaturated aldehyde derivative (g; % yield)	Bp, °C (mm)	^{1}H NMR, δ
10 (11.0; 0.072)	11.1 (0.075) 2.2 (0.015)[a]	15 3	**10** (3.9)	**43a,b** (8.7; 74)	104–127 (0.2)	**43a:** 1.3 (12 H, m), 3.6 (3 H, m), 4.4 (5 H, m), 7.6 (1 H, d)
13 (40.0; 0.38)	61.0 (0.41)	76	**13** (21.0)	**45a,b** (19.2)[b]	125–150 (1.0)	**45a:**[e] 1.4 (6 H, t, J = 7 Hz), 2.35 (3 H, s), 2.85 (2 H, d, J = 5 Hz), 3.6 (4 H, m), 4.7 (1 H, t, J = 5 Hz) **45b:**[e] 1.4 (3 H, t, J = 8 Hz), 2.3 (3 H, s), 4.1 (2 H, q, J = 7 Hz), 6.2 (1 H, d, J = 12 Hz), 7.4 (1 H, d, J = 12 Hz)
15 (25.0; 0.21)	35.0 (0.24)	45	**15** (14.4)	**46** (16; 70)	55–80 (0.2)	**46:** 1.2 (9 H, m), 2.2 (3 H, s), 2.65 (1 H, m), 3.55 (4 H, m), 4.5 (1 H, d)
16 (9.0; 0.05)	7.6 (0.05) 3.8 (0.026)[a]	9.5		**47a,b** (11.5; 95)[c]		**47a:** 1.2 (9 H, m), 2.8–4.2 (5 H, m), 4.4 (1 H, d), 7.4 (5 H, m)
17 (7.3; 0.05)	8.1 (0.055)	9.6		**48** (4; 29)[d]		**48:** 1.1–3.9 (19 H, m), 4.75 (1 H, d)
18 (19.8; 0.15)	24.3 (0.165)	28.8	**18** (7)	**49a,b** (7.5; 36)	120–140 (0.5)	**49a:** 1.0 (6 H, m), 2.0 (3 H, m), 2.8 (3 H, m), 3.5 (4 H, m), 4.1 (1 H, m), 4.7 (1 H, d)

[a] An additional amount of $HC(OEt)_3$ was added after heating overnight at 130 °C. [b] A mixture of **45a** and **45b** was obtained by short-path distillation; therefore, no yield was calculated. [c] Crude residue. [d] Obtained as an oil by chromatography on silica gel on elution with $CHCl_3$. [e] NMR spectrum was determined on fractionation of a mixture of **45a** and **45b; 45a,** bp 112–117 °C (0.5 mm); **45b,** bp 125–130 °C (0.5 mm).

(^{79}Br) and 245 (^{81}Br). MS Calcd for $C_9H_{10}BrNO_2$: 242.9895. MS Found: 242.9897.

Spectral and Analytical Properties of 26–30 and 50–53. Ethyl 2-Bromo-4-methylnicotinate (26): ^{1}H NMR ($CDCl_3$) δ 1.4 (3 H, t), 2.4 (3 H, s), 4.5 (2 H, q), 7.5 (1 H, d), and 8.25 (1 H, d); MS m/e (M^+) 243 (^{79}Br) and 245 (^{81}Br). MS Calcd for $C_9H_{10}BrNO_2$: 242.9895. MS Found: 242.9890.

2-Bromo-5-methylnicotinonitrile (27): ^{1}H NMR δ 2.4 (3 H, s), 7.75 (1 H, d), and 8.4 (1 H, d); MS m/e (M^+) 196 (^{79}Br) and 198 (^{81}Br). Anal. Calcd for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22. Found: C, 42.49; H, 2.61; N, 14.30.

2-Bromo-4-phenylnicotinonitrile (28): ^{1}H NMR ($CDCl_3$) δ 7.4 (1 H, d), 7.55 (5 H, s), and 8.5 (1 H, d). Anal. Calcd for $C_{12}H_7BrN_2$: C, 55.62; H, 2.72; N, 10.81. Found: C, 55.72; H, 2.78; N, 10.79.

2-Bromo-4-ethylnicotinonitrile (29): ^{1}H NMR ($CDCl_3$) δ 1.35 (3 H, t), 2.9 (2 H, q), 7.35 (1 H, d), and 8.5 (1 H, d); MS m/e (M^+) 210 (^{79}Br) and 212 (^{81}Br). Anal. Calcd for $C_8H_7BrN_2$: C, 45.52; H, 3.34; N, 13.27. Found: C, 45.65; H, 3.66; N, 13.27.

2-Bromo-5-methyl-4-phenylnicotinonitrile (30): ^{1}H NMR ($CDCl_3$) δ 2.15 (3 H, s), 7.4 (5 H, m), and 8.45 (1 H, s). Anal. Calcd for $C_{13}H_9BrN_2$: C, 57.16; H, 3.32; N, 10.26. Found: C, 56.88; H, 3.70; N, 10.16.

2-Bromo-4-methylnicotinonitrile (50): ^{1}H NMR ($CDCl_3$) δ 2.6 (3 H, s), 7.25 (1 H, d), and 8.35 (1 H, d); MS m/e (M^+) 196 (^{79}Br) and 198 (^{81}Br). Anal. Calcd for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22. Found: C, 42.58; H, 2.55; N, 14.38.

2-Bromo-4,5-dimethylnicotinonitrile (51): ^{1}H NMR ($CDCl_3$) δ 2.3 (3 H, s), 2.55 (3 H, s), and 8.2 (1 H, s); MS m/e (M^+) 210 (^{79}Br) and 212 (^{81}Br). Anal. Calcd for $C_8H_7BrN_2$: C, 45.52; H, 3.34; N, 13.27. Found: C, 45.34; H, 3.19; N, 13.32.

2-Bromo-3-cyano-5,6,7,8-tetrahydroisoquinoline (52): ^{1}H NMR ($CDCl_3$) δ 1.85 (4 H, p), 2.85 (4 H, m), and 8.2 (1 H, s). Anal. Calcd for $C_{10}H_9BrN_2$: C, 50.65; H, 3.82; N, 11.82. Found: C, 51.09; H, 3.82; N, 11.90.

2-Bromo-3-cyano-4,5-cyclopentenopyridine (53): ^{1}H NMR ($CDCl_3$) δ 2.2 (2 H, m), 3.1 (4 H, m), and 8.25 (1 H, s). Anal. Calcd for $C_9H_7BrN_2$: C, 48.45; H, 3.16; N, 12.56. Found: C, 48.37; H, 3.12; N, 12.52.

General Procedure for the Preparation of Compounds 31–34. The preparation of **31,** the *N*-(*N'*,*N'*-dimethylaminomethylene) derivative of the cyclohexylidenemalononitrile dimer, is presented as an example. To DMF acetal (13 g, 0.11 mol) and DMF (1.5 mL) was added cyclohexylidenemalononitrile (14.6 g, 0.1 mol) dropwise with stirring and ice cooling. After warming to room temperature overnight, the reaction mixture was poured into Et_2O (100 mL) and washed with H_2O (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was chromatographed on silica gel and the product eluted with 3% MeOH–$CHCl_3$ to yield 3.0 g of **31** (17%), mp 149–153 °C (from *n*-butyl chloride). Anal. Calcd for $C_{21}H_{25}N_5$: C, 72.59; H, 7.25; N, 20.16. Found: C, 72.23; H, 7.44; N, 20.31.

Compounds **32, 33,** and **34** were prepared in a manner similar to **31** in yields of 25 (mp 145–146.5 °C, from *n*-butyl chloride), 62 (mp 83–85 °C from ligroin), and 60% (mp 128–130 °C, from ligroin), respectively.

Table VI. Experimental Details for HBr–AcOH Cyclization Reaction

β,γ-Unsaturated aldehyde equivalent (g)	AcOH, mL	30% HBr–AcOH, mL	Product (g; % yield)[a]	Bp (mm) or mp, °C
20 (7.4)	50	50	**26** (5.2; 58)	110–112 (0.7)
21 (8.8)	30	50	**27**[b] (0.4; 5)[c]	109–111
22 (13.5)	100	100	**28**[b] (3.8; 22)[d]	122–125
23 (4.0)	20	40	**29**[b] (2.4; 16)[c]	64–65
24 (1.3)	3.7	5.6	**30**[b] (0.15; 3)[c]	123–124
43a,b (8.7)	60	60	**25** (4.3; 40)	115–130 (0.25)
44 (11.2)	50	100	**27**[b] (3.0; 15)[c]	109–111
45a,b (19.2)	80	160	**50**[b] (1.0; 23)[c]	109–111
46 (16.0)	50	100	**51**[b] (6.3; 29)[c]	93–95
47a,b (11.5)	100	100	**30**[b] (5.7; 42)[c]	123–124
48 (4.0)	10	15	**52**[b] (2.0; 15)[c]	128.5–130.5
49 (7.5)	20	35	**53**[b] (3.4; 15)[c]	103–105

[a] Yields reported are for the overall two-step process. [b] The nicotinonitrile derivatives were obtained by chromatography on silica gel and the products eluted with $CHCl_3$. [c] Purified by recrystallization from ligroin. [d] Purified by recrystallization from cyclohexane.

High-resolution mass spectral and NMR data for compounds **31–34** are presented in Table II. Anal. Calcd for $C_{19}H_{21}N_5$ (**32**): C, 71.44; H, 6.63; N, 21.93. Found: C, 71.47; H, 6.97; N, 21.76. Anal. Calcd for $C_{15}H_{17}N_5$ (**33**): C, 67.39; H, 6.37; N, 26.20. Found: C, 67.74; H, 6.61; N, 26.23. Anal. Calcd for $C_{17}H_{21}N_5$ (**34**): C, 69.12; H, 7.17; N, 23.71. Found: C, 69.46; H, 7.48; N, 23.82.

Preparation of Compound 38. To **37** (1.6 g, 0.0067 mol) and DMF (5 mL) was added DMF acetal (0.8 g, 0.007 mol). After stirring overnight at room temperature, the mixture was poured in Et_2O (50 mL) and washed with H_2O (2 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness to yield 1.8 g (91%) of **38:** mp 120–121 °C (from ligroin); ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t), 1.25 (3 H, s), 1.75 (5 H, m), 2.4 (2 H, bs), 3.1 (6 H, d), 6.0 (1 H, q), and 7.8 (1 H, s). Anal. Calcd for $C_{17}H_{21}N_5$: C, 69.12; H, 7.17; N, 23.71. Found: C, 69.32; H, 7.35; N, 23.99. The exact mass was 295.1803 (calcd, 295.1797).

Preparation of the Cyclopentylidenemalononitrile Dimer (36). Following the procedure of Weir and Hyne[11] for the synthesis of **35** and **37**, compound **36** was prepared by essentially the same manner in 38% yield, mp 178–182 °C (from H_3CCN). Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 73.03; H, 6.31; N, 21.50. The exact mass was 264.1365 (calcd, 264.1375).

Stability of Compounds 31–34 and 38. Refluxing a solution of dimer **34** (150 mg) in xylene overnight gave by ^1H NMR spectroscopy a mixture of 16% of **34** and 84% of **38**. After heating **38** (50 mg) for 3 days in refluxing xylene, no change was observed in the ^1H NMR spectrum. On refluxing **31, 32,** and **33** overnight in xylene, no change was observed by ^1H NMR spectroscopy.

Preparation of 2-Bromo-5-methylnicotinic Acid (39). A mixture of **25** (7.1 g, 0.03 mol) and 10% NaOH solution (500 mL) was heated on a steam bath with stirring. After 3 h, the solution was cooled and neutralized with 12 N HCl. After cooling in an ice bath, the mixture was filtered to yield 5.6 g (89%) of **39:** mp 170–171 °C (from H_2O–MeOH); ^1H NMR (Me_2SO-d_6) δ 2.35 (3 H, s), 7.9 (1 H, d), and 8.3 (1 H, d); MS *m/e* (M^+) 215 (^{79}Br) and 217 (^{81}Br). Anal. Calcd for $C_7H_6BrNO_2$: C, 38.91; H, 2.80; N, 6.48. Found: C, 39.22; H, 2.97; N, 6.59.

Preparation of 2-Bromo-4-methylnicotinic Acid (40). Compound **26** (12.1 g, 0.05 mol) in 10% NaOH (500 mL) yielded 9.3 g (87%) of **40:** mp 173–174 °C (from H_2O); ^1H NMR (Me_2SO-d_6) δ 2.35 (3 H, s), 7.4 (1 H, d), and 8.3 (1 H, d); MS *m/e* (M^+) 215 (^{79}Br) and 217 (^{81}Br). Anal. Calcd for $C_7H_6BrNO_2$: C, 38.91; H, 2.80; N, 6.48. Found: C, 39.09; H, 2.88; N, 6.39.

Preparation of 2-Bromo-5-methyl-3-trifluoromethylpyridine (41). Into a steel bomb was placed **39** (5.0 g, 0.023 mol), SF_4 (31 g, 0.29 mol), and HF (5.3 mL). The contents were heated at 120 °C for 8 h. After cooling to room temperature, the bomb was opened and the contents were poured onto saturated Na_2CO_3 solution and extracted with $CHCl_3$ (3 × 100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue distilled at 45–49 °C (0.1 mm) to yield 4 g (59%) of **41:** ^1H NMR ($CDCl_3$) δ 2.35 (3 H, s), 7.7 (1 H, d), and 8.25 (1 H, d); ^{19}F NMR ($CDCl_3$) +63.1 (s); MS *m/e* (M^+) 239 (^{79}Br) and 241 (^{81}Br). MS Calcd for $C_7H_5BrF_3N$: 238.9558. MS Found: 238.9555.

Preparation of 2-Bromo-4-methyl-3-trifluoromethylpyridine (42). Similarly, compound **40** (9.3 g, 0.05 mol), SF_4 (58 g, 0.53 mol), and HF (9.8 mL) yielded 6.2 g (60%) of **42:** bp 45–50 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 2.80 (3 H, q), 7.2 (1 H, d), and 8.3 (1 H, d); MS *m/e* (M^+) 239 (^{79}Br) and 241 (^{81}Br). Anal. Calcd for $C_7H_5BrF_3N$: C, 35.02; H, 2.10; N, 5.84. Found: C, 34.56; H, 2.22; N, 5.65.

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