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Synthesis of 1-Arylmethyl-2-(cyanomethyl)aziridines and Their Ring Transformation into Methyl *N*-(2-Cyanocyclopropyl)benzimidates

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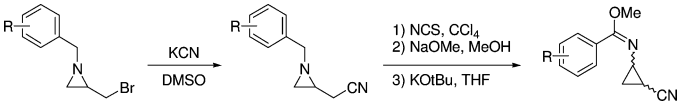

1-Arylmethyl-2-(cyanomethyl)aziridines were prepared in high yields from the corresponding 2-(bromomethyl)aziridines upon treatment with potassium cyanide in DMSO. Ring opening of the aziridine moiety with *N*-chlorosuccinimide in CCl_4 and subsequent treatment of the thus formed 4-chloro-3-(*N*-chloro-*N*-(α,α-dichlorobenzyl)amino)butanenitriles with sodium methoxide in methanol resulted in novel methyl *N*-(2-chloro-1-(cyanomethyl)ethyl)benzimidates, although in low yields. The latter γ-chloro nitriles were smoothly converted into methyl *N*-(2-cyanocyclopropyl)benzimidates as precursors of biologically relevant β-ACC derivatives through a 1,3-cyclization protocol by reaction with potassium *tert*-butoxide in THF.

Introduction

The search for new pathways toward amino nitriles as precursors of the corresponding amino acids is an important challenge in organic synthesis.[1] The interesting pharmacological properties of, e.g., β- and γ-amino acids and their use in the synthesis of the corresponding β- and γ-peptides have, especially in the past decade, renewed the interest of organic chemists.[2] The conformationally restricted 2-aminocyclopropanecarboxylates (β-ACC's) comprise a peculiar class of β-amino acids with interesting applications in peptide chemistry, hence the recent efforts in the literature toward new and improved synthetic approaches.[3]

The combination of an aziridine moiety and a nitrile group in the same molecule results in a versatile substrate, allowing the synthesis of a whole variety of functionalized amino nitriles due to the reactivity of the constrained aziridine ring. However, the synthesis of e.g., 2-(cyanomethyl)aziridines has hardly been investigated in the literature up to now. In this report, an efficient and straightforward approach toward novel 2-(cyanomethyl)-aziridines with high synthetic potential is described in a one-step procedure starting from 1-arylmethyl-2-(bromomethyl)-aziridines. The former 2-(cyanomethyl)aziridines were transformed into biologically interesting *N*-(2-cyanocyclopropyl)benzimidates as β-ACC precursors via intermediate 4-chloro-3-(*N*-chloro-*N*-(α,α-dichlorobenzyl)amino)butanenitriles and methyl *N*-(2-chloro-1-(cyanomethyl)ethyl)benzimidates, respectively. Convenient approaches toward β-ACC derivatives are limited due to the push−pull substitution on the cyclopropane ring, and therefore, an appropriate *N*-protecting group has to be introduced during the synthesis. This is the first report of the use of γ-(leaving-group)-β-aminobutanenitriles as substrates for the synthesis of β-aminocyclopropyl nitriles via an intramolecular 1,3-cyclization protocol.

Results and Discussion

1-Alkyl-2-(bromomethyl)aziridines **1** are suitable synthetic equivalents for the aziridinylmethyl cation, providing easy access

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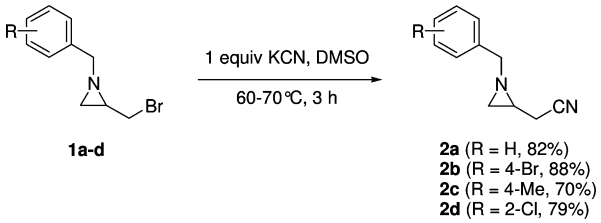
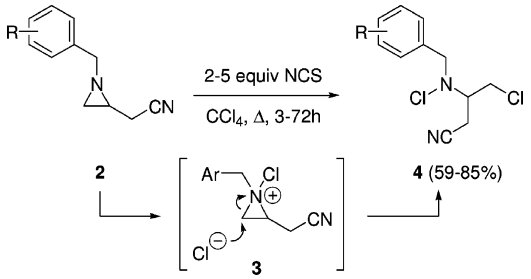
SCHEME 1



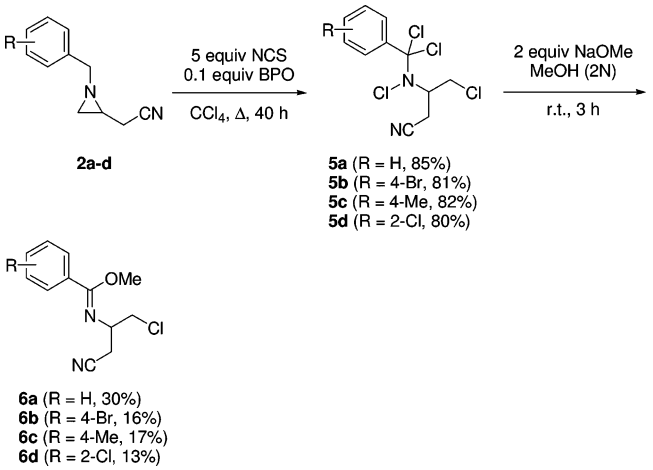
to 2-substituted 1-alkylaziridines upon treatment with carbon-centered (lithium dialkylcuprates) as well as heteroatom-centered nucleophiles.[4] Further elaboration of this approach using a different type of carbon-centered nucleophiles, i.e., cyanide, resulted in the preparation of the corresponding new 2-(cyanomethyl)aziridines **2** in excellent yields upon treatment of 2-(bromomethyl)aziridines **1** with 1 equiv of potassium cyanide in DMSO and heating at 60−70 °C for 3 h (Scheme 1). Only one similar 2-(cyanomethyl)aziridine has been reported in the literature, i.e., 1-*tert*-butyl-2-(cyanomethyl)aziridine, prepared from 4-*tert*-butylamino-3-hydroxybutyronitrile upon mesylation and treatment with a base, although the reaction mixture contained only 10% of the desired aziridine besides two elimination products.[5] The present methodology offers a very efficient and convenient alternative for the preparation of a variety of 2-(cyanomethyl)aziridines as valuable substrates for the synthesis of β- and γ-amino nitriles with potential applications in medicinal chemistry. Other examples of 2-(cyanomethyl)aziridines (e.g., with a rather complex 1- or 2-substituent in their structure) are scarce in the literature,[6] and no general synthetic approach has been available to date. In one case, a 2-(iodomethyl) substituent was transformed into a 2-(cyanomethyl) group in a complex 1,2,3-trisubstituted aziridine toward the synthesis of biologically relevant aziridinomitosenes.[6b]

2-(Cyanomethyl)aziridines **2** constitute versatile substrates for further elaboration due to the presence of the constrained aziridine moiety. To evaluate ring-opening reactions toward valuable amino nitriles, the reactivity of aziridines **2** with regard to *N*-chlorosuccinimide (NCS) was investigated. Activation of the aziridine ring by means of an electrophilic chlorine delivered by NCS followed by ring opening of the resulting *N*-chloroaziridinium intermediate **3** by a nucleophilic chloride (derived from in situ liberated chlorine gas from NCS) would give rise to the corresponding 3-amino-4-chlorobutanenitriles **4** (Scheme 2). Alternatively, formation of *N*-chloroamines **4** can be the result of a radical-mediated ring-opening process instead of nucleophilic ring opening of aziridinium salts **3**. Treatment of 2-(cyanomethyl)aziridines **2** with 2 equiv of NCS in refluxing CCl_4 did not always give reproducible results, as sometimes a partial conversion was observed, whereas in other cases using exactly the same reaction conditions all the starting material was consumed (Scheme 2). Furthermore, a set of two experiments was performed simultaneously using 2 equiv of NCS in refluxing CCl_4, and in one of them a catalytic amount of

SCHEME 2



SCHEME 3



potassium iodide (0.1 equiv) was added to see whether iodide could promote this conversion. However, addition of potassium iodide only resulted in a decrease of reactivity when compared to the experiment without potassium iodide, and substantial amounts of the starting material were recovered (29−33%). Presumably, this can be explained considering a halophilic attack of iodide onto the electrophilic *N*-chloro atom of the aziridinium intermediates. An increase in the amount of reagent (2.5, 3, 3.5, and 5 equiv of NCS) usually resulted in higher conversion rates (>25%). Attempts to purify amino nitriles **4** by means of column chromatography for complete characterization failed due to the unstable nature of these compounds. The use of NCS for the *N*-chlorination of *N*-benzyl-*N*-butylamine in pentane toward the corresponding *N*-chloroamine has been described previously.[7]

Surprisingly, after treatment of aziridines **2** with an excess of 5 equiv of NCS in CCl_4 and heating under reflux for 3 days, the substrate was completely consumed and the reaction mixture contained one major product in 61−88% yield, which was identified as 4-chloro-3-(*N*-chloro-*N*-(dichloro(aryl)methyl)-amino)butanenitrile **5**. Since the double chlorination in the benzylic position of compounds **5** probably proceeded through radical intermediates, benzoylperoxide (BPO) was added in order to improve the reaction conditions. Eventually, trichlorinated amino nitriles **5** were obtained in optimal yields and acceptable purity for further elaboration using 5 equiv of NCS and 0.1 equiv of BPO after reflux for 40 h (Scheme 3). The radical chlorination of benzylic hydrogens by NCS has recently been reported in the literature.[8] Due to the unstable nature of *N*-chloro amines **5**, although quite stable in carbon tetrachloride

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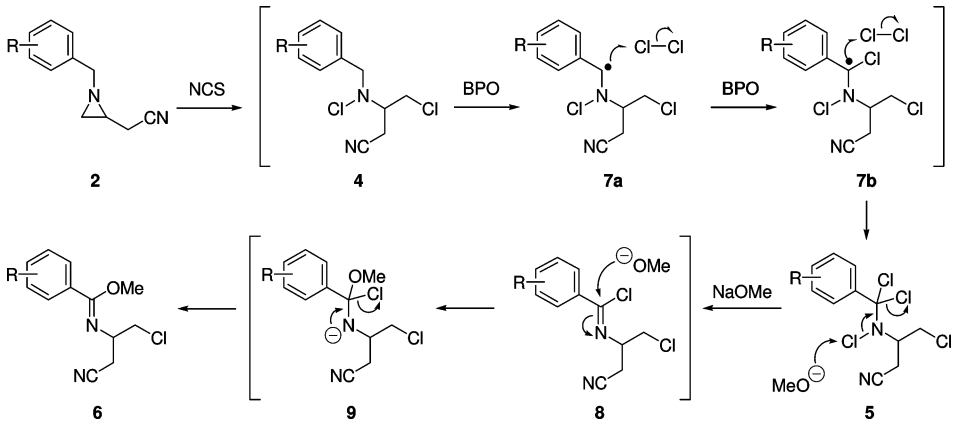
TABLE 1. Spectroscopic Evidence for Compounds 4 and 5

	R´ = NC, Cl	H, N, Ar, R´	Cl, N, Ar, R´ **4**	Cl, Cl, Cl, N, Ar, R´ **5**
^{1}H NMR ($CDCl_3$, ppm)		3.7 – 3.9	4.2 – 4.3	-
^{13}C NMR ($CDCl_3$, ppm)		50 – 51	64 – 65	95 – 97

SCHEME 4



solution, these compounds had to be used immediately for further elaboration after immediate characterization by means of NMR and IR. Distinction between amines **4** and **5** can be made based on spectroscopic analysis (Table 1). Treatment of the latter amines **5a**−**d** with 2 equiv of sodium methoxide in methanol (2 N) resulted in rather complex reaction mixtures, although spectral analysis of these mixtures (NMR and IR) clearly showed the presence of an imidate functionality. Despite the low yields, the novel methyl benzimidates **6a**−**d** were isolated in high purity by means of column chromatography on silica gel (Scheme 3). For imidates **6**, only one stereoisomer was obtained, which was assigned to the *Z*-isomer due to steric hindrance. Imidates are useful building blocks in organic synthesis, especially for heterocyclic compounds and as precursors for biologically active amidines, hence the interest in their preparation.[9,10] Furthermore, several imidates are of interest in agrochemistry for their fungicidal and herbicidal properties.[11]

In Scheme 4 a tentative proposal for the reaction mechanism has been suggested. Treatment of aziridines **2** with an excess of NCS affords 3-amino-4-chlorobutanenitriles **4** through ring opening of the intermediate aziridinium salt **3** (as depicted in Scheme 2) or via a radical reaction, followed by double chlorination of the radical intermediates **7** at the benzylic position (initiated by BPO) resulting in 4-chloro-3-(*N*-chloro-*N*-(dichloro(aryl)methyl)amino)butanenitrile **5**. It is clear that further research is required for a complete understanding of the reaction mechanism of the ring opening of aziridines by means of NCS. Abstraction of the electrophilic *N*-chloro atom by methoxide via a halophilic protocol affords imidoyl chloride **8**, which subsequently undergoes nucleophilic addition across the imino bond by the excess of methoxide toward imidates **6** (Scheme 4).

The presence of a γ-chloro nitrile moiety in imidates **6** allows the 1,3-intramolecular ring closure toward cyclopropyl nitriles upon α-deprotonation with respect to the nitrile moiety using an appropriate base and subsequent chloride expulsion. Several reaction conditions were evaluated, such as 1 equiv of lithium diisopropyl amide (LDA) in THF and 1.5 equiv of KOtBu in diethyl ether, *tert*-butyl alcohol, and tetrahydrofuran. In the former case (LDA), the desired cyclopropyl nitriles could be prepared in good yields, although some minor impurities were present in the reaction mixtures. When KOtBu was used in tBuOH, no reaction occurred, whereas with KOtBu in Et_2O a complex reaction mixture was obtained. However, the premised cyclization proceeded very nicely utilizing 1.5 equiv of KOtBu in THF and reflux for 5−9 h (Scheme 5). In this way, methyl *N*-(2-cyanocyclopropyl)benzimidates **10a**−**d** were prepared for the first time by means of an elegant 1,3-cyclization protocol via intermediates **11** starting from 4-chlorobutanenitriles **6a**−**d**. The ratio of *cis*- and *trans*-isomers of compounds **10** was determined by ^{1}H NMR and GC analysis. These constrained carbocycles **10** can be considered as precursors of biologically relevant β-aminocyclopropanecarboxylates (β-ACC's), which are important building blocks in the synthesis of peptides with improved properties and in SAR studies,[12] since a few specific examples are known regarding the enzymatic hydrolysis of cyclopropane nitriles toward the corresponding carboxylic acids by *Rhodococcus* sp.[13] It is known that β-ACC's are extremely sensitive to ring-opening reactions and that they are only stable

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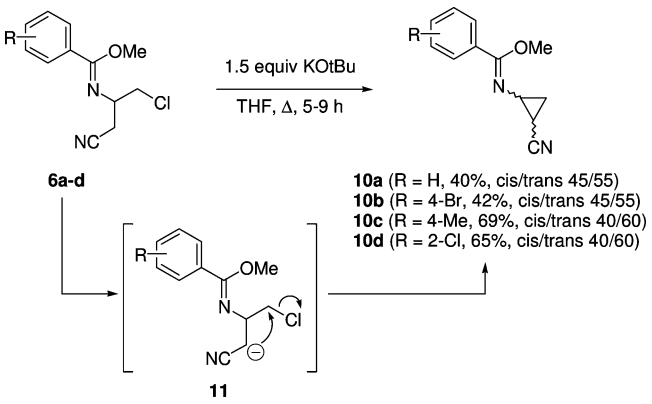
SCHEME 5



if the amino moiety is protected by at least one electron-withdrawing group,[14] in this case an imidate functionality.

In conclusion, 1-arylmethyl-2-(cyanomethyl)aziridines have been prepared from the corresponding 2-(bromomethyl)aziridines in a very efficient and straightforward approach using KCN in DMSO. The former aziridines are valuable substrates for the synthesis of biologically relevant β- and γ-amino nitriles. 1-Arylmethyl-2-(cyanomethyl)aziridines were ring opened toward 4-chloro-3-(*N*-chloro-*N*-(α,α-dichlorobenzyl)amino)butanenitriles in high yields utilizing NCS in CCl_4, and these reactive *N*-chloro amines were subsequently transformed into methyl *N*-(2-chloro-1-(cyanomethyl)ethyl)benzimidates, although in low yields. Furthermore, methyl *N*-(2-chloro-1-(cyanomethyl)ethyl)benzimidates proved to be excellent substrates for the 1,3-intramolecular ring closure by means of KOtBu in THF toward biologically important *N*-(2-cyanocyclopropyl)benzimidates as β-ACC precursors. The net conversion of this methodology concerns a ring transformation of an aziridine into a cyclopropylamine derivative.

Experimental Section

1-(2-Chlorobenzyl)-2-(cyanomethyl)aziridine 2d. The synthesis of 1-(2-chlorobenzyl)-2-(cyanomethyl)aziridine **2d** is described as a representative example for the synthesis of 2-(cyanomethyl)-aziridines **2**. 1-(2-Chlorophenyl)methyl-2-(bromomethyl)aziridine **1d** (1.30 g, 5 mmol) and potassium cyanide (0.33 g, 5 mmol, 1 equiv) were heated in dimethyl sulfoxide (25 mL) at 65 °C for 3 h. Subsequently, the reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (2 × 35 mL) and brine (35 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent afforded 1-(2-chlorobenzyl)-2-(cyanomethyl)aziridine **2d**. Yield 79%, colorless oil. Flash chromatography on silica gel: hexane/EtOAc 3/2, $R_f = 0.35$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (1H, d, $J = 5.6$ Hz), 1.90 (1H, d, $J = 3.3$ Hz), 1.88−1.93 (1H, m), 2.48−2.62 (2H, m), 3.58 and 3.65 (2H, 2d, $J = 14.9$ Hz), 7.19−7.38 and 7.59−7.62 (3H and 1H, 2m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 33.3, 34.4, 60.7, 117.2, 127.0, 128.4, 129.25 and 129.32, 133.0, 136.1. IR (NaCl, cm^{-1}): $\nu_{CN} = 2253$. MS (70 eV): *m*/*z* 207/9 ($M^+ + 1$; 100); 125/7 (78). Anal. Calcd for $C_{11}H_{11}ClN_2$: C, 63.93; H, 5.36; N, 13.55. Found: C, 64.15; H, 5.53; N, 13.71.

4-Chloro-3-(*N*-chloro-*N*-(dichloro(phenyl)methyl)amino)butanenitrile 5a. The synthesis of 4-chloro-3-(*N*-chloro-*N*-(dichloro-(phenyl)methyl)amino)butanenitrile **5a** is described as a representative example for the synthesis of butanenitriles **5**. To a stirred solution of 1-benzyl-2-(cyanomethyl)aziridine **2a** (0.17 g, 1 mmol) in CCl_4 (4 mL) was added NCS (0.67 g, 5 equiv) and BPO (0.02 g, 0.1 equiv), and the resulting mixture was heated under reflux for 40 h. Cooling of the reaction mixture at −20 °C (1 h), filtration (succinimide), and evaporation of the solvent afforded 4-chloro-3-(*N*-chloro-*N*-(dichloro(phenyl)methyl)amino)butanenitrile **5a**. Yield 85%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.87 and 2.91 (2H, 2dd, $J = 16.4$, 6.1, 5.4 Hz), 3.71−3.83 (2H, m), 4.46−4.53 (1H, m), 7.42−7.56 and 8.03−8.14 (5H, 2m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 44.8, 60.4, 96.1, 116.6, 129.1, 131.5, 129.5, 147.1. IR (NaCl, cm^{-1}): $\nu_{CN} = 2254$. Due to the lability of compounds **5** in general, no suitable mass spectral data could be obtained.

Methyl *N*-(2-Chloro-1-(cyanomethyl)ethyl)-4-methylbenzimidate 6c. The synthesis of methyl *N*-(2-chloro-1-(cyanomethyl)-ethyl)-4-methylbenzimidate **6c** is described as a representative example for the synthesis of benzimidates **6**. To nitrile **5c** (0.33 g, 1 mmol) was added a solution of NaOMe in MeOH (1 mL, 2 equiv, 2 N), and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was poured into water (5 mL) and extracted with Et_2O (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent afforded a mixture containing methyl *N*-(2-chloro-1-(cyanomethyl)ethyl)-4-methylbenzimidate **6c**, which was purified by means of column chromatography (hexane/EtOAc 3/1). Yield 17%, yellow oil. Flash chromatography on silica gel: hexane/EtOAc 3/1, $R_f = 0.29$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (3H, s), 2.60 and 2.62 (2H, 2dd, $J = 16.4$, 6.5, 5.2 Hz), 3.47 and 3.54 (2H, 2dd, $J = 11.0$, 6.9, 6.1 Hz), 3.81−3.87 (1H, m), 3.83 (3H, s), 7.23−7.25 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 23.6, 47.1, 53.8, 56.5, 117.4, 127.5, 129.4, 128.6, 140.1, 165.3. IR (NaCl, cm^{-1}): $\nu_{C\equiv N} = 2254$, $\nu_{C=N} = 1661$. MS (70 eV): *m*/*z* 251/3 ($M^+ + 1$; 100). Anal. Calcd for $C_{13}H_{15}ClN_2O$: C, 62.28; H, 6.03; N, 11.17. Found: C, 62.50; H, 6.22; N, 10.96.

Methyl *N*-(2-Cyanocyclopropyl)benzimidate 10a. The synthesis of methyl *trans*-*N*-(2-cyanocyclopropyl)benzimidate *trans*-**10a** and methyl *cis*-*N*-(2-cyanocyclopropyl)benzimidate *cis*-**10a** is described as a representative example for the synthesis of cyclopropyl nitriles **10**. To an ice-cooled solution of benzimidate **6a** (0.04 g, 0.2 mmol) in dry THF (2 mL) was added KOtBu (0.04 g, 1.5 equiv), and the resulting mixture was heated under reflux for 5 h. The reaction mixture was poured into water (2 mL) and extracted with Et_2O (3 × 2 mL). Washing of the combined organic extracts with brine (1 mL), drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent afforded a mixture of methyl *trans*-*N*-(2-cyanocyclopropyl)benzimidate *trans*-**10a** and methyl *cis*-*N*-(2-cyanocyclopropyl)benzimidate *cis*-**10a**, which were separated by preparative thin-layer chromatography (hexane/EtOAc 9/1), resulting in very small amounts (insufficient for ^{13}C NMR). Methyl *trans*-*N*-(2-cyanocyclopropyl)benzimidate *trans*-**10a**: Yellow oil. TLC on silica gel: hexane/EtOAc 9/1, $R_f = 0.14$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35−1.40 (2H, m), 1.63 (1H, ddd, $J = 8.0$, 7.4, 3.1 Hz), 3.38 (1H, ddd, $J = 6.5$, 5.9, 3.1 Hz), 3.72 (3H, s), 7.47−7.49 (5H, m). MS (70 eV): *m*/*z* 200 (M^+; 28), 199 (23), 185 (4), 173 (5), 169 (9), 160 (4), 146 (6), 132 (8), 120 (4), 105 (100), 77 (39), 51 (9). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.17; H, 6.24; N, 13.74. Methyl *cis*-*N*-(2-cyanocyclopropyl)benzimidate *cis*-**10a**: Yellow oil. TLC on silica gel: hexane/

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EtOAc 9/1, $R_f = 0.20$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31−1.43 (2H, m), 1.59−1.66 (1H, m), 3.24 (1H, ddd, $J = 6.7, 6.7, 5.0$ Hz), 3.84 (3H, s), 7.45−7.49 (5H, m). MS (70 eV): *m*/*z* 200 (M^+; 29), 199 (23), 185 (4), 173 (7), 169 (10), 160 (5), 146 (7), 132 (9), 120 (5), 105 (100), 77 (40), 51 (9). Spectral data derived from the mixture of *cis*- and *trans*-**10a**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.9, 16.2, 16.6, 37.0, 40.1, 53.5, 53.9, 119.7, 120.8, 128.1, 128.6, 128.7, 130.1, 130.3, 164.1, 164.3. IR (NaCl, cm^{-1}): $\nu_{C\equiv N} = 2238$, $\nu_{C=N} = 1661$. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.16; H, 6.20; N, 13.71.

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Supporting Information Available: General information and all spectroscopic data of compounds **2a**−**c**, **5b**−**d**, **6a**,**b**,**d**, and **10b**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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