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An approach to 2-cyanopyrrolidines bearing a chiral auxiliary

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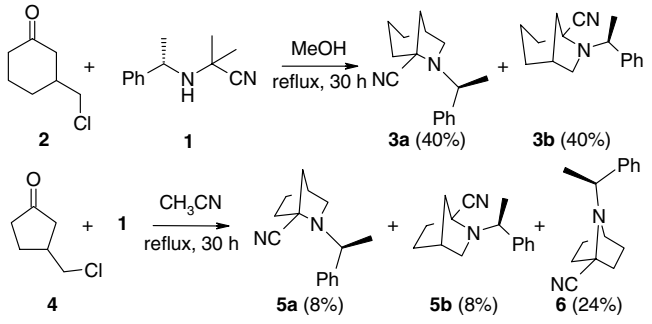
Abstract—The reaction of 2-methyl-2-((1-phenylethyl)amino)propanenitrile with different γ-halocarbonyl compounds is investigated. The influence of different parameters such as the nature of the substrate and solvent, is discussed. The reaction is considered as a convenient route to 2-cyanopyrrolidines in the case of aliphatic γ-halocarbonyl compounds possessing a reasonably reactive carbonyl group. In many cases, the products can be obtained as single enantiomers. It is shown that cyclopropyl ketones can also react with 2-methyl-2-((1-phenylethyl)amino)propanenitrile to give 2-cyanopyrrolidines. A mechanistic scheme is proposed in order to explain the experimental facts observed.

1. Introduction

2-Cyanopyrrolidines have been used as building blocks for the synthesis of cage systems, alkaloids and their analogues, amino acids and other biologically active compounds.[1] One of the most interesting applications of 2-cyanopyrrolidines in organic synthesis is their transformation to proline analogues.[2] Therefore, general methods for the synthesis of 2-cyanopyrrolidines are of great interest. In most cases these compounds are chiral, and stereoselective approaches to their synthesis are often required.

Recently, we found[3] that compound **1** reacted with 3-chloromethylcyclohexanone **2** to give diastereomeric 2-cyanopyrrolidines **3a** and **3b** in a good yield (Scheme 1). 3-Chloromethylcyclopentanone **4**, which possesses a less reactive carbonyl group compared to compound **2**, gave 2-cyanopyrrolidines **5a** and **5b** in lower yield; the main product of the reaction was the unexpected compound **6**. The diastereomers obtained in both reactions shown in Scheme 1 were separated by column chromatography.

The reaction of α-aminonitrile **1** with γ-halocarbonyl compounds might have great potential as a stereoselective approach to 2-cyanopyrrolidines and their derivatives. The



Scheme 1.

presence of the chiral auxiliary, the α-phenylethylamine moiety, might allow a separation of diastereomers and/or chiral induction in further transformations of the 2-cyanopyrrolidines. On the other hand, this chiral auxiliary can be easily removed by hydrogenation. Therefore, we decided to investigate the scope of the reaction of **1** with γ-haloketones and γ-haloaldehydes. The carbonyl compounds **7**–**11** with a different reactivity of the carbonyl group were selected as model substrates in addition to **2** and **4**.

2. Results and discussion

Several parameters, namely, the nature of the substrate and the solvent, temperature, reagents ratio, etc. might

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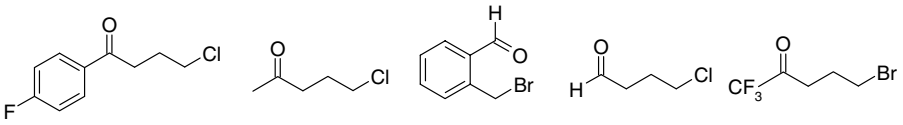


7 8 9 10 11

influence the reaction of α-aminonitrile **1** with different γ-chlorocarbonyl compounds.

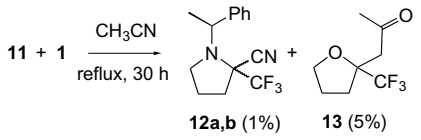
We first varied the reaction conditions using ketones **2** and **4** as the model substrates. Isolation of the products by column chromatography and investigation of the reaction mixtures by NMR and GC–MS were used to study the reaction progress. In a previous paper,[3] we reported only the optimized conditions for both the reactions of **2** and **4**; herein, we summarize all our experiments. It was found that the solvent nature has a dramatic influence on the reaction progress and outcome. No 2-cyanopyrrolidines **5** and **6** were formed from **4** in low-polar solvents such as benzene or chloroform; these results are in accordance with those reported in the literature[4] for the analogous transformation. Only trace amounts of **5** and **6** were formed from **4** in methanol, whereas moderate yields of these products were obtained in other polar solvents such as acetonitrile, dimethylsulfoxide or 2-propanol. In the case of ketone **2**, bridged 2-cyanopyrrolidines **3** were obtained in high yields either in methanol, acetonitrile or DMSO, although the yield of **3** was diminished in benzene as the solvent.

Increasing the reaction time and/or temperature mainly influenced the rate of the reaction and not the product distribution and yields, both of **3** and **5** and **6**.

The substrate nature appeared to be the dominating factor for determining the reaction progress. Carbonyl group reactivity towards nucleophiles was shown to be highly critical for achieving good yields of 2-cyanopyrrolidines.

While the reactive γ-chloroketone **2** gave 2-cyanopyrrolidines in a good total yield, compound **7** possessing a very low-electrophilic carbonyl group did not give the corresponding 2-aryl-2-cyanopyrrolidines at all. Even after a prolonged reaction time, only the starting compound was recovered.

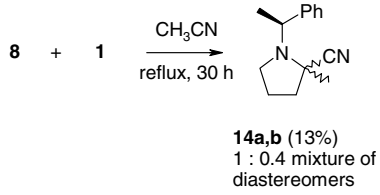
Reaction of **1** with ketone **11** possessing a highly reactive carbonyl group led to a complex mixture of products. Traces of the trifluoromethyl-substituted 2-cyanopyrrolidines **12a** and **12b** were detected in the reaction mixture by means of NMR and LC–MS. One of these diastereomers was isolated although in a very low yield (less than 1%). Compound **13** was also isolated in a 5% yield (Scheme 2). We believe that high reactivity of ketone **11** led to its reaction with any of the nucleophiles present in the reaction mixture, resulting in very low yields of the expected 2-cyanopyrrolidines.



12a,b (1%) **13** (5%)

Scheme 2.

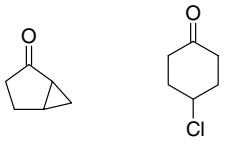
Moderate yields of the corresponding 2-cyanopyrrolidines were obtained from ketones **4** (Scheme 1) and **8** (Scheme 3[†]).



14a,b (13%)
1 : 0.4 mixture of diastereomers

Scheme 3.

As we have reported earlier,[3] unexpected product **6** was mainly formed in the case of **4**. We suggested that cyclopropane **15** and 4-chlorocyclohexanone **16** could be intermediates in the formation of compound **6**. Therefore the reaction of **1** with compounds **15** and **16** was performed to test this hypothesis. In the case of **16**, the yields of compounds **5a**, **5b** and **6** (10%, 7% and 23%, respectively) were practically identical to those for the reaction of compound **4**. Cyclopropane **15** also gave cyanopyrrolidines **5a**, **5b** and **6** when reacted with **1** in the presence of 1.05 equiv of α-phenylethylamine hydrochloride despite the yields of the products were lower (2%, 2% and 13% for **5a**, **5b** and **6**, respectively). No reaction proceeded without a chloride ion donor.

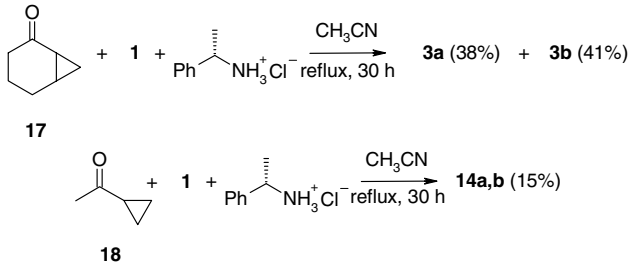


15 **16**

These results allowed us to suggest that other cyclopropanes might be used as starting compounds for the synthesis of 2-cyanopyrrolidines by a cascade sequence: cyclopropane ring opening—Strecker reaction—intramolecular nucleophilic substitution. It indeed proved to be true, at least for cyclopropyl ketones **17** and **18** (Scheme 4[‡]).

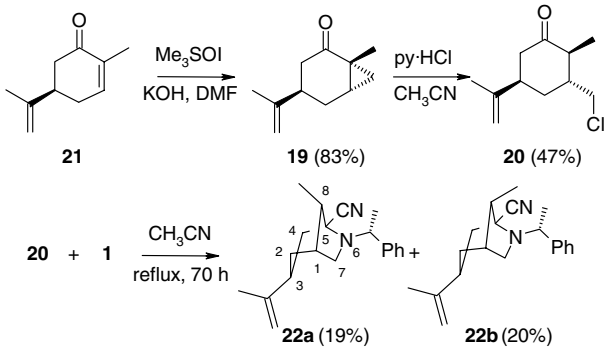
Other cyclohexanone derivatives **19** and **20**, which we have tested in this reaction were obtained from (*R*)-carvone **21** by the method described in the literature.[5] The reaction

[†] Total yield of **14** is 63% by NMR.
[‡] Yield of **14** is detected by NMR.



Scheme 4.

of **20** with reagent **1** proceeded much more slowly than the reaction of **2**; after 70 h of reflux, we obtained product **22** in a 39% yield (Scheme 5).



Scheme 5.

Since the starting γ-chloroketone **20** was enantiomerically pure, we expected only one stereoisomer of product **22** to be formed. Surprisingly, compound **22** was obtained as a 1:1 mixture of diastereomers **22a** and **22b**, which were successfully separated by means of semi-preparative HPLC.

The reaction between cyclopropane derivative **19** and **1** under the conditions described above only yielded starting compounds after 40 h of refluxing. No products **22a** and **22b** were detected.

The carbonyl group of aldehydes is far more reactive than that of ketones, therefore, it was not surprising that the reaction of **1** with aldehyde **10** proceeded already at an ambient temperature. The expected 2-cyanopyrrolidine **23** was obtained in 66% yield as 1:0.7 mixture of diastereomers (Scheme 6).

Scheme 6.

The reaction of aminonitrile **1** with aromatic aldehyde **9** also proceeded at an ambient temperature as in the case of **10**. However, a complex mixture of unidentified compounds was obtained. We were only able to isolate isoindolone **24** by column chromatography in a 12% yield.[6] Supposedly, the unstable isoindole **25** was formed as the main product of the reaction, which underwent oxidation by air oxygen forming **24**. We trapped isoindole **25** by a Diels–Alder reaction with maleimide **26**; compound **27** was obtained in a 40% yield (Scheme 7).

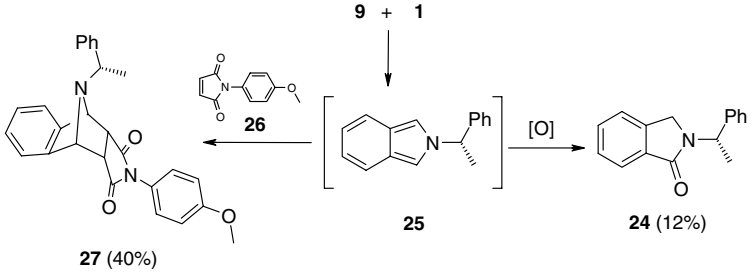
We believe that it was aromaticity of isoindole **25** that led to its formation instead of the corresponding 2-cyanopyrrolidine.

The mechanistic considerations described in the literature[4,7] allowed us to suggest aminonitriles, such as **28**, as the key intermediates of the reaction of **1** with γ-halocarbonyl compounds. Scheme 8 illustrates this for the reaction of **1** with one of the enantiomers of ketone **4**. In the case of cyclic ketones, only one diastereomer of aminonitrile **28** (namely, **28a**) can undergo the cyclization, while the second, **28b**, has to be converted to **28a**.

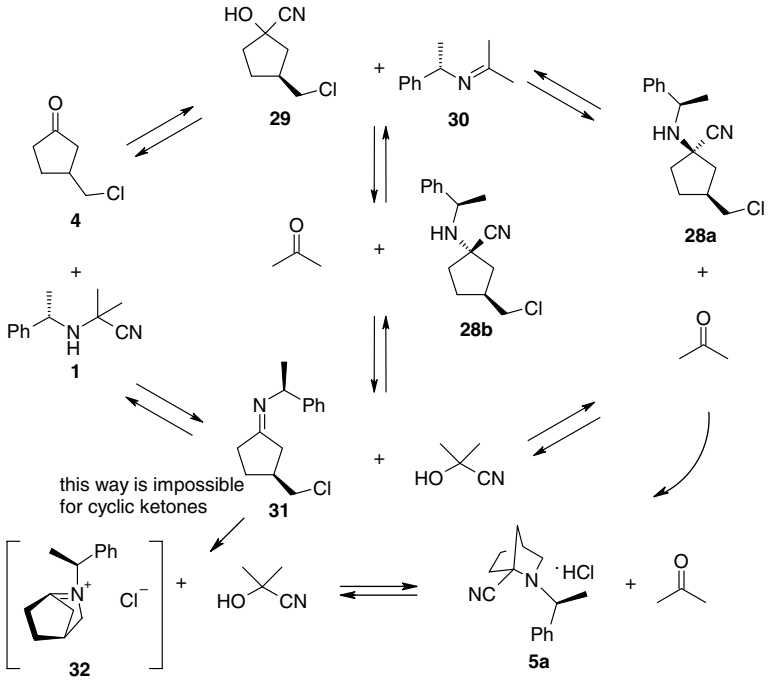
Indirect proof of this scheme is the observation of intermediates of type **28**.[7] We also observed intermediates **30** and **31** by GS–MS analysis of the reaction mixture.

In our opinion, it is critical for the success of the reaction, that **1** provides hydrogen cyanide and α-phenylethylamine in a low concentration. A higher concentration of these nucleophiles might cause undesirable side reactions.[3,4,7]

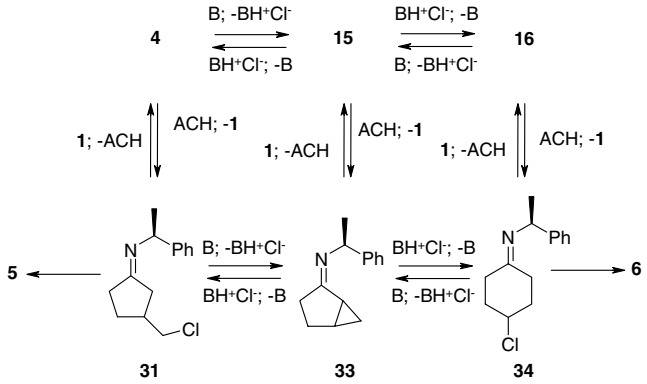
The results obtained in this study prompted us to make some additional comments and refinements to the scheme described above. The pathway through iminium salts mentioned in a previous work[4] seems to not be dominant:



Scheme 7.



Scheme 8.



Scheme 9. (ACH = acetone cyanohydrin).

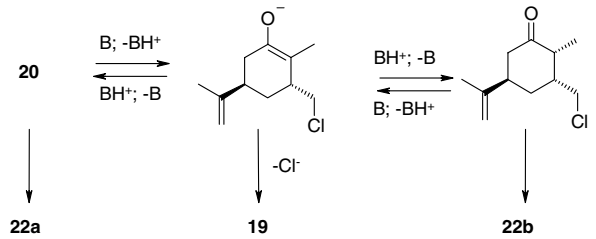
cyclic γ-chloroketones reacted with **1** as efficiently as acyclic ones, although the first should form highly strained anti-Bredt intermediates such as **32**. The experimental facts also point out that additional equilibria should be accounted for, namely, formation of the cyclopropane derivatives, as illustrated by Scheme 9. Any of the amines present in the reaction mixture can play the role of the base (B) necessary for these transformations.

The structure of the unexpected product **6** obtained from compound **4**, observation of **15** and **33** by GS–MS analysis of the reaction mixture and formation of 2-cyanopyrrolidines by the reaction of cyclopropanes **15**, **17** and **18** with reagent **1** are all evidences for these suggestions.

This mechanistic scheme also explains the epimerization during the synthesis of 2-cyanopyrrolidines from 2-substituted cyclohexanone **20**. It proceeds due to reversible deprotonation of the starting γ-chloroketone, which is the first step in the formation of the corresponding cyclopropane derivative **19** (Scheme 10).

3. Conclusions

Reaction of α-aminonitrile **1** with γ-halocarbonyl compounds is the result of a subtle balance of the reactivity of the substrate, solvent nature and specific properties of **1** as the source of α-phenylethylamine and hydrogen cyanide (Fig. 1). This approach can be considered as a



Scheme 10.

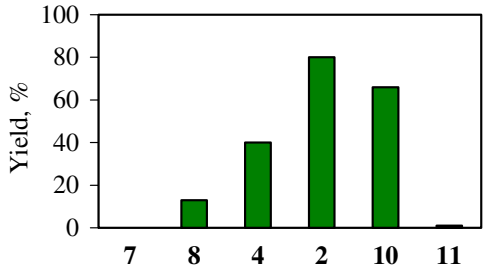


Figure 1. Total yields of 2-cyanopyrrolidines obtained from different γ-halocarbonyl compounds (the substrates are given in the order of increasing reactivity of their carbonyl group towards nucleophiles).

convenient route to 2-cyanopyrrolidines in the case of aliphatic γ-halocarbonyl compounds. The presence of a chiral auxiliary—α-phenylethylamine moiety—allows chromatographic separation of stereoisomers in many cases; hence the synthesis of enantiomerically pure products is possible.

4. Experimental

All air- and moisture-sensitive reactions were performed under an argon atmosphere using a standard Schlenk technique. The solvents were purified according to a standard procedures.[8] 2-Methyl-2-((1-phenylethyl)amino)propanenitrile **1**,[3] 3-chloromethylcyclohexanone **2**,[5] 3-chloromethylcyclopentanone **4**,[5] 5-chloro-2-pentanone **8**,[5] 2-(bromomethyl)benzaldehyde **9**,[9] 4-chlorobutyraldehyde **10**,[10] 1,1,1-trifluoro-5-bromo-2-pentanone **11**,[11] bicyclo[3.1.0]hexan-2-one **15**,[3] 4-chlorocyclohexanone **16**,[12] bicyclo[4.1.0]heptan-2-one **17**[3] were prepared according to the procedures described in the literature. All other starting materials were purchased from Acros, Merck, Aldrich and Fluka chemicals. Melting points are uncorrected. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) stationary phase. ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on Varian Unity Plus 400 spectrometer at 400.1, 376.7 and 100.7 MHz, respectively. Chemical shifts are reported in parts per million downfield from TMS (^{1}H and ^{13}C NMR) or C_6F_6 (^{19}F NMR) as an internal standards. IR spectra were obtained on Nicolet Nexus 470 spectrometer. ν_{max} (cm^{-1}) values in IR spectra are given for the main absorption bands. Mass spectra were recorded on Agilent 1100 LCMSD SL instrument with chemical ionization (CI). Optical rotation values were measured on a Perkin-Elmer 341 polarimeter.

4.1. (1*R*,4*R*,6*S*)-4-Isopropenyl-1-methylbicyclo[4.1.0]-heptan-2-one 19

Trimethylsulfoxonium iodide (50.4 g, 0.229 mol) and 12.9 g (0.229 mol) of potassium hydroxide were dissolved in 330 ml of DMF at 30–40 °C under vigorous stirring. The clear solution formed was cooled to 20 °C, and the solution of 32.8 g (0.219 mol) of (*R*)-carvone in 70 ml of DMF was added. The obtained reaction mixture was stirred for 3 h and allowed to stand overnight, then poured into water and extracted with dichloromethane. The combined extracts were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure to give 30 g (0.183 mol) of **20**, which was used for the next step without further purification. For spectral and physical data see Ref. 13.

4.2. (2*S*,3*R*,5*R*)-3-(Chloromethyl)-5-isopropenyl-2-methylcyclohexanone 20

Pyridinium hydrochloride (15 g, 130 mmol) was added to a solution of 10.6 g (65 mmol) of compound **20** in 70 ml of acetonitrile. The mixture was refluxed for 36 h, then poured into water and extracted with ether. The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (benzene–ethyl acetate (13:1) as an eluent) to give 6.1 g (31 mmol, 47%) of **21**, which was used for the further transformations. To obtain an analytical sample of **21**, the product was chromatographed once more [hexane–benzene (2:1) as an eluent]. $[\alpha]_D = -18.8$ (*c* 0.41, MeOH). ^{1}H NMR ($CDCl_3$), δ: 4.92 (s, 1H, C(CH_3)=CH_2), 4.75 (s, 1H, C(CH_3)=CH_2), 3.68 (m, 2H, CH_2Cl), 2.8 (m, 1H), 2.65 (dd, 1H, $J = 14.8$ and 3.2 Hz), 2.51 (dd, 1H, $J = 14.8$ and 6.0 Hz), 2.39 (m, 1H), 2.09 (m, 2H, CH_2), 1.93 (m, 1H), 1.82 (s, 3H, C(CH_3)=CH_2), 1.30 (d, 3H, $J = 6.8$ Hz, 2-CH_3). ^{13}C NMR ($CDCl_3$), δ: 205.0 (*C*=O), 144.6 (*C*=CH_2), 111.5 (C=*C*H_2), 46.9, 45.2, 42.3, 39.7, 38.6, 29.5, 20.8, 10.5. IR: 1712 (ν C=O). MS (*m*/*z*): 201 (MH^+), 165 (M^+−Cl). Anal. Calcd for $C_{11}H_{17}ClO$: C, 65.83; H, 8.54; Cl, 17.66. Found: C, 65.52; H, 8.25; Cl, 17.87.

4.3. Reaction of 1 with γ-halocarbonyl compounds (general procedure)[3]

Aminonitrile **1** (1.05 equiv) was added to a solution of 1 equiv of γ-halocarbonyl compound in dry acetonitrile. The mixture obtained was refluxed or was allowed to stand under an argon atmosphere under the conditions listed in Table 1, then poured into excess of 10% sodium hydroxide solution and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was analysed by NMR and GS–MS and/or chromatographed.

4.4. Reaction of 1 with cyclopropyl ketones (general procedure)

Aminonitrile **1** (1.05 equiv) and 1.05 equiv of (*S*)-α-phenylethylamine hydrochloride were added to a solution of 1 equiv of cyclopropyl ketone in dry acetonitrile. The

Table 1. Reaction of α-aminonitrile **1** with different substrates

Entry no.	Substrate	Reaction conditions		Eluent for the chromatography	Products (yields, %)
		Temperature	Time (h)		
1	**7**	Reflux	70	Hexane–ethyl acetate (2:1)	—
2	**8**	Reflux	30	Hexane–ethyl acetate (2:1)	**14a**(9), **14b**(4)[a]
3	**9**	Ambient	50	Hexane–ethyl acetate (5:1)	**21**(12)
4	**10**	Ambient	150	Hexane–ethyl acetate (5:1)	**23a**(39), **23b**(27)
5	**11**	Reflux	10	Hexane–ethyl acetate (20:1)	**12a**(1), **13**(5)
6	**15**	Reflux	30	The same as for **4**[3]	**5a**(2), **5b**(2), **6**(13)
7	**16**	Reflux	30	The same as for **4**[3]	**5a**(10), **5b**(7), **6**(23)
8	**17**	Reflux	30	The same as for **2**[3]	**3a**(39), **3b**(39)
9	**18**	Reflux	30	The same as for **8**	**14a**(11), **14b**(4)[b]
10	**19**	Reflux	40	Hexane–ethyl acetate (5:1)	—
11	**20**	Reflux	70	The same as for **19**	**22a**(19), **22b**(20)

[a] Total yield of **14** is 63% by NMR.
[b] Yield of **14** is detected by NMR.

mixture obtained was refluxed under an argon atmosphere under the conditions listed in Table 1 and then worked up as described above.

4.5. 1-[(1*S*)-1-Phenylethyl]-2-(trifluoromethyl)pyrrolidine-2-carbonitrile 12a

This was obtained from 1,1,1-trifluoro-5-bromo-2-pentanone **11** in a 1% yield. ^{1}H NMR ($CDCl_3$), δ: 7.13–7.24 (m, 5H), 4.44 (q, $J = 6.8$ Hz, 1H, C*H*CH$_3$), 2.89 (q, $J = 7.2$ Hz, 1H, 5-CH_2), 2.75 (m, 1H, 5-CH_2), 2.39 and 2.32 (m, 2H, 3-CH_2), 1.78 (m, 2H, 4-CH_2), 1.49 (d, $J = 6.8$ Hz, 3H, CHCH_3). ^{13}C NMR ($CDCl_3$), δ: 143.2 (*ipso*-C_6H_5), 131.0 (q, $J = 252$ Hz, CF_3), 128.3, 126.9, 126.5, 117.2 (*C*N), 68.2 (*C*-2), 55.5 (*C*HCH$_3$), 45.3, 35.7, 23.0 (*C*H$_3$), 14.7. ^{19}F NMR ($CDCl_3$), δ: 84,6 (s, CF_3). IR: 2232 (ν C≡N). MS (EI, *m*/*z*): 268 (M^+), 105. Anal. Calcd for $C_{14}H_{15}F_3N_2$: C, 62.68; H, 5.64; N, 10.44. Found: C, 62.39; H, 5.25; N, 10.42.

4.6. 1-[2-(Trifluoromethyl)tetrahydrofuran-2-yl]acetone 13

This was obtained from 1,1,1-trifluoro-5-bromo-2-pentanone **11** in a 5% yield. ^{1}H NMR ($CDCl_3$), δ: 3.85 (d, $J = 7.2$ Hz, 2H, OCH_2), 2.88 (d, $J = 14.4$ Hz, 1H, C(O)CH_2), 2.41 (d, $J = 14.4$ Hz, 1H, C(O)CH_2), 2.34 (m, 1H), 2.11 (s, 3H, CH_3), 2.05 (m, 1H), 1.94 (m, 2H). ^{13}C NMR ($CDCl_3$), δ: 201.2 (CO), 124.6 (q, $J = 281.5$ Hz, CF_3), 81.9 (q, $J = 27.6$ Hz, CCF_3), 69.2 (OCH_2), 43.2, 31.1 (*C*H$_3$), 28.5, 24.6. ^{19}F NMR ($CDCl_3$), δ: 84,7 (s, CF_3). IR: 1716 (ν C=O). MS (EI, *m*/*z*): 127 (M^+-CF_3), 69 (CF_3^+), 43 (CH_3CO^+). Anal. Calcd for $C_8H_{11}F_3O_2$: C, 48.98; H, 5.65. Found: C, 48.75; H, 5.44.

4.7. 2-Methyl-1-((1*S*)-1-phenylethyl)pyrrolidine-2-carbonitrile 14

This was obtained as a mixture of (2*R*)- and (2*S*)-diastereomers (**14a**:**14b** = 1:0.4) from 5-chloro-2-pentanone **8** in a 13% yield. ^{1}H NMR ($CDCl_3$), δ: 7.22–7.39 (m, 5H, C_6H_5 of **14a** and 5H, C_6H_5 of **14b**), 3.94 (q, $J = 6.7$ Hz, 1H, C*H*CH$_3$ of **14a**), 3.85 (q, $J = 7.0$ Hz, 1H, C*H*CH$_3$ of **14b**), 3.22 (m, 1H, 5-CH_2 of **14a**), 2.89 (m, 1H, 5-CH_2 of **14b**), 2.80 (dd, $J = 17.5$ and 8.0 Hz, 5-CH_2 of **14a**), 2.48 (dd, $J = 17.5$ and 8.0 Hz, 5-CH_2 of **14b**), 2.35 (m, 1H, 3-CH_2 of **14b**), 2.29 (m, 1H, 3-CH_2 of **14a**), 1.96 (m, 1H, 3-CH_2 of **14a**), 1.85 (m, 3H, 3-CH_2 and both 4-CH_2 of **14a**), 1.74 (m, 2H, 4-CH_2 of **14b**), 1.67 (s, 3H, CH_3 of **14b**), 1.49 (d, 3H, $J = 6.0$ Hz, CHCH_3 of **14a**), 1.49 (d, 3H, $J = 6.5$ Hz, CHCH_3 of **14b**), 1.03 (s, 3H, CH_3 of **14a**). ^{13}C NMR ($CDCl_3$), δ: 145.6 (*ipso*-C_6H_5 of **14a**), 144.3 (*ipso*-C_6H_5 of **14b**), 128.4, 128.3, 127.4, 127.3, 127.2, 127.1, 121.5 (*C*N of **14a**), 120.9 (*C*N of **14b**), 61.1 (*C*-2 of **14a**), 61.0 (*C*HCH$_3$ of **14b**), 59.3 (*C*-2 of **14b**), 58.6 (*C*HCH$_3$ of **14a**), 52.1 (5-*C*H$_2$ of **14b**), 49.1 (5-*C*H$_2$ of **14a**), 41.7 (3-*C*H$_2$ of **14b**), 40.4 (3-*C*H$_2$ of **14a**), 27.0 (*C*H$_3$ of **14b**), 25.5 (*C*H$_3$ of **14a**), 23.7 (CH*C*H$_3$ of **14b**), 20.9 (CH*C*H$_3$ of **14a**), 20.8 (4-*C*H$_2$ of **14b**), 19.9 (4-*C*H$_2$ of **14a**). To assign the signals in NMR spectra and to confirm the cyclic structure of **11**, ^{1}H–^{1}H COSY, IPT, HSQC and HMBC experiments were carried out. IR: 2219 (ν C≡N). MS (*m*/*z*): 188 (M^+-CN), 105. Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.09; H, 8.25; N, 12.94.

4.8. 3-Isopropenyl-8-methyl-6-[(1*R*)-1-phenylethyl]-6-azabicyclo[3.2.1]octane-5-carbonitrile 22

This was obtained as 1:1 mixture of (1*R*,3*R*,5*S*,8*S*)- (**22a**) and (1*R*,3*R*,5*S*,8*R*)- (**22b**) diastereomers from ketone **19** in a 39% yield.[§] A sample of compound **22** was separated by semi-preparative HPLC to give pure diastereomers **22a** and **22b** (Zorbax SB-C18 semi-preparative column, CH_3CN–H_2O (70:30) as an eluent, 30 °C, flow rate—1.7 ml/min, retention times 27.96 min (**22a**) and 29.66 min (**22b**)).

4.9. (1*R*,3*R*,5*S*,8*S*)-3-Isopropenyl-8-methyl-6-[(1*R*)-1-phenylethyl]-6-azabicyclo[3.2.1]octane-5-carbonitrile 22a

^{1}H NMR ($CDCl_3$), δ: 7.37 (d, $J = 7.5$ Hz, 2H, *o*-C_6H_5), 7.32 (t, $J = 7.5$ Hz, 2H, *m*-C_6H_5), 7.24 (t, $J = 7.2$ Hz, 1H, *p*-C_6H_5), 4.76 (s, 1H, $CH_3C{=}CH_2$), 4.75 (s, 1H, $CH_3C{=}CH_2$), 4.11 (q, $J = 6.7$ Hz, 1H, C*H*(C_6H_5)CH$_3$), 3.10 (dd, $J = 10.0$ and 5.6 Hz, 1H, *exo*-7-CH_2), 2.52 (m, 1H, 8-C*H*), 2.25 (d, $J = 10.0$ Hz, 1H, *endo*-7-CH_2),

[§] (*R*)-Isomer of **1** was used for the reaction.

2.13–2.33 (m, 3H, 3-C*H*, *endo*-4-CH_2 and 1-C*H*), 1.85 (dd, $J = 13.6$ and 12.4 Hz, 1H, *exo*-4-CH_2), 1.75 (s, 3H, CH_3C=CH_2), 1.66 (t, $J = 13.2$ Hz, 1H, *endo*-2-CH_2), 1.61 (d, $J = 6.5$ Hz, 3H, CH(C_6H_5)CH_3), 1.36 (m, 1H, *exo*-2-CH_2), 1.23 (d, $J = 7.0$ Hz, 3H, 8-CHCH_3). ^{13}C NMR ($CDCl_3$), δ: 147.6 (*C*=CH$_2$), 145.5 (*ipso*-C_6H_5), 128.6 (*m*-C_6H_5), 127.4 (C_6H_5), 127.3 (C_6H_5), 123.5 (*C*N), 110.2 (C=*C*H$_2$), 60.6 and 60.5 (5-*C* and *C*H(C_6H_5)CH$_3$), 56.6 (7-CH_2), 44.9 (8-*C*H), 37.3 (3-*C*H), 37.0 (1-C*H*), 31.5 (4-*C*H$_2$), 28.4 (2-*C*H$_2$), 24.1 (CH(C_6H_5)*C*H$_3$), 20.7 (*C*H$_3$C=CH$_2$), 10.3 (8-CH*C*H$_3$). To assign the signals in NMR spectra, ^{1}H–^{1}H COSY, HSQC, HMBC and NOE experiments were carried out. IR: 2234 (ν C≡N). MS (*m*/*z*): 295(MH$^+$), 191. Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.94; H, 8.62; N, 9.20. The results of combustion elemental analysis were obtained for the mixture of diastereomers **22a** and **22b**.

4.10. (1*R*,3*R*,5*S*,8*R*)-3-Isopropenyl-8-methyl-6-[(1*R*)-1-phenylethyl]-6-azabicyclo[3.2.1]octane-5-carbonitrile 22b

^{1}H NMR ($CDCl_3$), δ: 7.29–7.38 (m, 4H, *o*-C_6H_5 and *m*-C_6H_5), 7.25 (t, $J = 7.2$ Hz, 1H, *p*-C_6H_5), 4.78 (s, 1H, CH_3C=C*H*$_2$), 4.70 (s, 1H, CH_3C=C*H*$_2$), 4.18 (q, $J = 6.8$ Hz, 1H, C*H*(C_6H_5)CH$_3$), 3.10 (dd, $J = 9.6$ and 6.0 Hz, 1H, *exo*-7-CH_2), 2.46 (dd, $J = 13.5$ and 5.0 Hz, 1H, *endo*-4-CH_2), 2.26 (d, $J = 10$ Hz, 1H, *endo*-7-CH_2), 2.22 (m, 1H, *endo*-2-CH_2), 2.04 (br s, 1H, 1-C*H*), 1.98 (q, $J = 6.8$ Hz, 1H, 8-C*H*), 1.77 (t, $J = 13.0$ Hz, 1H, *exo*-4-CH_2), 1.68 (s, 3H, CH_3C=CH$_2$), 1.64 (m, 1H, 3-C*H*), 1.61 (d, $J = 6.5$ Hz, 3H, CH(C_6H_5)CH_3), 1.47 (t, $J = 12.8$ Hz, 1H, *exo*-2-CH_2), 1.30 (d, $J = 7.0$ Hz, 3H, 8-CHCH_3). ^{13}C NMR ($CDCl_3$), δ: 147.3 (*C*=CH$_2$), 145.6 (*ipso*-C_6H_5), 128.6 (*m*-C_6H_5), 127.2 (C_6H_5), 127.1 (C_6H_5), 122.5 (*C*N), 110.2 (C=*C*H$_2$), 62.3 (5-*C*), 59.4 (*C*H(C_6H_5)CH$_3$), 53.9 (7-CH_2), 50.0 (8-*C*H), 39.7 (1-*C*H), 39.3 (4-*C*H$_2$), 37.9 (3-*C*H), 36.9 (2-CH$_2$), 23.9 (CH(C_6H_5)*C*H$_3$), 20.6 (*C*H$_3$C=CH$_2$), 16.4 (8-CH*C*H$_3$). To assign the signals in the NMR spectra, ^{1}H–^{1}H COSY, HSQC, HMBC and NOE experiments were carried out. IR: 2234 (ν C≡N). MS (*m*/*z*): 295 (MH$^+$), 191. Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.94; H, 8.62; N, 9.20. The results of combustion elemental analysis were obtained for the mixture of diastereomers **22a** and **22b**.

4.11. 1-((1*R*)-1-Phenylethyl)pyrrolidine-2-carbonitrile 23

This was obtained from 4-chlorobutyraldehyde **10** in 66% yield as 1:0.7 mixture of (2*R*)- and (2*S*)-diastereomers.[§] ^{1}H NMR ($CDCl_3$), δ: 7.2–7.4 (m, 5H, C_6H_5 of **23a** and m, 5H, C_6H_5 of **23b**), 4.15 (d, $J = 6.5$ Hz, 1H, 2-C*H* of **23b**), 3.65 (q, $J = 6.7$ Hz, 1H, C*H*CH$_3$ of **23a**), 3.59 (q, $J = 6.3$ Hz, 1H, C*H*CH$_3$ of **23b**), 3.48 (d, $J = 6.5$ Hz, 1H, 2-C*H*), 3.27 (m, 1H, 5-CH_2 of **23a**), 2.69 (td, $J = 9.5$ and 3.8 Hz, 1H, 5-CH_2 of **23b**), 2.55 (q, $J = 8.3$ Hz, 1H, 5-CH_2 of **23a**), 2.30 (q, $J = 9.0$ Hz, 5-CH_2 of **23b**), 2.22 (m, 1H, 3-CH_2 of **23b**), 2.16 (m, 1H, 3-CH_2 of **23b**), 2.00 (m, 4H, 3-CH_2 and 4-CH_2 of **23a**), 1.88 (m, 1H, 4-CH_2 of **23b**), 1.80 (m, 1H, 4-CH_2 of **23b**), 1.44 (d, $J = 7.0$ Hz, 3H, CHCH_3 of **23a**), 1.43 (d, $J = 7.5$ Hz, 3H, CHCH_3 of **23b**). ^{13}C NMR ($CDCl_3$), δ: 144.5 (*ipso*-C_6H_5 of **23b**), 143.9 (*ipso*-C_6H_5 of **23a**), 128.7, 128.6, 127.6, 127.4, 127.2, 121.0, 118.0 (*C*N of **23a**), 117.8 (*C*N of **23b**), 61.8 (*C*HCH$_3$ of **23b**), 61.6 (*C*HCH$_3$ of **23b**), 53.2 (2-*C*H of **23a**), 52.0 (2-*C*H of **23b**), 50.4 (5-*C*H$_2$ of **23b**), 48.8 (5-*C*H$_2$ of **23a**), 29.8 (3-*C*H$_2$ of **23b**), 29.5 (3-*C*H$_2$ of **23a**), 23.1 (CH*C*H$_3$), 23.0 (CH*C*H$_3$), 21.9 (4-*C*H$_2$), 21.8 (4-*C*H$_2$). IR: 2220 (ν C≡N). MS (*m*/*z*): 174 (M$^+$−CN), 105. Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 78.17; H, 7.69; N, 14.33.

4.12. 2-((1*R*)-1-Phenylethyl)isoindolin-1-one 24

This was obtained from 2-(bromomethyl)benzaldehyde **9** in a 12% yield.[§] Mp = 140–143 °C (lit.[6] 142–144 °C). For spectral and physical data see Ref. 6.

4.13. (3a*R*,4*S*,9*R*,9a*S*)-2-(4-Methoxyphenyl)-10-[(1*R*)-1-phenylethyl]-3a,4,9,9a-tetrahydro-1*H*-4,9-epiminobenzo[*f*]-isoindole-1,3-dione 27

Compound **1**[§] (180 mg) and 0.20 g of *N*-(*p*-methoxyphenyl)maleimide were added to a solution of 122 mg (0.61 mmol) of 2-(bromomethyl)benzaldehyde **9** in 10 ml of dry acetonitrile. The reaction mixture was allowed to stand in an argon atmosphere for 72 h. The solvent was removed by evaporation, and the residue was chromatographed with hexane–ethyl acetate (1:1) as an eluent to give 105 mg of compound **27** (0.25 mmol, 40%). Mp = 87–88 °C. $[\alpha]_D = +88.5$ (*c* 0.87, MeOH). ^{1}H NMR (CD_3OD), δ: 7.24 (m, 9H), 6.70 (d, 2H, $J = 8.0$ Hz, $C_6H_4OCH_3$), 6.22 (d, 2H, $J = 8.5$ Hz, $C_6H_4OCH_3$), 4.74 (br m, 1H, 4-C*H* or 9-C*H*), 4.40 (br m, 1H, 9-C*H* or 4-C*H*), 3.85 (dd, $J = 10.4$ and 5.2 Hz, 1H, 3a-C*H* or 9a-C*H*), 3.77 (br m, 1H, 9a-C*H* or 3a-C*H*), 3.63 (s, 3H, OCH_3), 3.16 (br m, 1H, C*H*CH$_3$), 1.32 (d, $J = 6.5$ Hz, CHCH_3) Signals at ^{1}H NMR spectrum are broadened and in some cases doubled probably due to slow inversion at N-10.[14] They are sharpened upon heating the sample to 50 °C. ^{13}C NMR (CD_3OD), δ: 176.0 (C=O), 175.9 (C=O), 159.6 (4′-$C_6H_4OCH_3$), 143.9 (*ipso*-C_6H_5), 141.0, 140.9, 128.4, 127.8 ($C_6H_4OCH_3$), 127.52, 127.48, 127.3, 126.8, 124.0, 123.0 (br s), 122.9 (br s), 113.6 (1′-C_6H_4OMe), 66.1 (*C*-4 or *C*-9), 65.6 (*C*-9 or *C*-4), 56.4 (*C*HCH$_3$), 54.5 (O*C*H$_3$), 46.89 and 46.88 (*C*-3a and *C*-9a), 21.3 (CH*C*H$_3$). To assign the signals in NMR spectra, ^{1}H–^{1}H COSY, HSQC and HMBC experiments were carried out. IR (KBr): 1774 (ν_{as} C=O), 1713 (ν_s C=O). MS (*m*/*z*): 425 (MH$^+$), 222, 118, 105. Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.40; H, 5.70; N, 6.60. Found: C, 76.02; H, 5.98; N, 6.24.

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