SUPPORTING INFORMATION

Synthesis of novel β-aminocyclobutanecarboxylic acid derivatives
by a solvent-free aza-Michael addition and subsequent ring closure

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Section 1: Reaction of malononitrile 6e in DMF with benzophenone imine

Upon reaction of malononitrile 6e in DMF a different reactivity towards benzophenone imine compared to malonates 6a-d was observed. Treatment of 2-(3-chloro-2,2-dimethylpropylidene)-malononitrile 6e with 1.1 equiv of benzophenone imine in the presence of K₂CO₃ in DMF under mild heating conditions (45 °C) gave rise to the formation of two reaction products, more specifically cyclobutane i and tetrahydropyridine ii, in a ratio of 36/74 (¹H NMR analysis) (Scheme a). The formation of tetrahydropyridine ii, which was isolated in 36% yield, is the result of a ring expansion of the functionalized cyclobutane i caused by the strong electron-withdrawing effects of the two geminal cyano groups which reduce the stability of the small-membered ring. When the reaction of malononitrile 6e and benzophenone imine was performed at room temperature, the ratio of the reaction products was reversed and the main component found in the crude reaction mixture was β-ACBC derivative i. Unfortunately, all attempts to isolate cyclobutane i in pure form via crystallization and/or column chromatography were unsuccessful.

**Scheme a**

\[
\begin{align*}
&\text{Cl} & & \text{DMF, r.t., 18.5 h} & & \text{60%} \\
&\text{CN} & & & & \\
&\text{CN} & & & & \\
&\text{CN} & & & & \\
&\text{NH} & & & & \\
&\text{Ph} & & & & \\
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&\text{Ph} & & & & \\
&\text{CN} & & & & \\
&\text{CN} & & & & \\
&\text{i} & & & & \\
&\text{ii} & & & & \\
\end{align*}
\]

\[6e + 1.1 \text{equiv} \text{NH} \xrightarrow{2 \text{equiv K}_2\text{CO}_3} \text{DMF, r.t., 18.5 h} \quad \text{i/ii: 4/1}
\]

\[\text{ii (36%)}
\]
Synthesis of 2,2-diphenyl-5,5-dimethyl-4,5-dihydro-2H-pyridine-3,3-dicarbonitrile ii.

To a solution of 2-(3-chloro-2,2-dimethylpropylidene)malononitrile 6e (1.5 mmol, 1 equiv) in DMF (10 mL), benzophenone imine (1.65 mmol, 1.1 equiv) and K$_2$CO$_3$ (3 mmol, 2 equiv) were added. The reaction mixture was stirred at 45 °C temperature for 17 hours, poured in CH$_2$Cl$_2$ (10 ml) and washed with brine (3x 10 mL). Subsequently, the organic fraction was dried over MgSO$_4$ and after removal of the drying agent by filtration, concentrated in vacuo. After recrystallisation from MeOH, pure 2,2-diphenyl-5,5-dimethyl-4,5-dihydro-2H-pyridine-3,3-dicarbonitrile ii was obtained as white crystals.

2,2-Diphenyl-5,5-dimethyl-4,5-dihydro-2H-pyridine-3,3-dicarbonitrile ii: Yield 36%. White crystals. Mp 182.5-183.7 °C. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 1.28 (6H, s (broad)); 2.33 (2H, s (broad)); 7.29-7.40 (8H, m); 7.62 (2H, s (broad)); 8.01 (1H, s). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 27.1; 33.4; 38.4; 39.3; 69.6; 115.7; 128.0; 128.3; 128.4; 169.3. IR (ATR, cm$^{-1}$): $\nu_{CN}$ = 2258; $\nu_{C=N}$ = 1664. MS (ES, pos. mode): $m/z$ (%): 314 (M+H$^+$, 100). Anal. Calcd for C$_{21}$H$_{19}$N$_3$: C 80.48, H 6.11, N 13.41. Found: C 80.37, H 5.96, N 13.43.

2-(Diphenylmethylideneamino)-3,3-dimethylcyclobutane-1,1-dicarbonitrile i: $^1$H NMR spectral data obtained from the analysis of the crude reaction mixture containing 80% cyclobutane i and 20% tetrahydropyridine ii. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 0.97 (3H, s); 1.34 (3H, s); 2.37 (1H, d, $J$ = 12.7 Hz); 2.64 (1H, d, $J$ = 12.7 Hz); 4.23 (1H, s); 7.15-7.81 (10H, m).
Section 2: Thermal stability of cyclobutane 9a in DMF

The instability of functionalised cyclobutane i at elevated temperatures in DMF, leading to a ring expansion towards tetrahydropyridine ii, prompted us to investigate the thermal stability of cyclobutanedicarboxylate 9a by heating this compound for two hours in DMF at 160 °C under microwave irradiation. Although the ring expansion to the corresponding tetrahydropyridine was expected, the presence of this heterocyclic compound in the crude reaction mixture could not be established. Cyclobutane 9a was prone to ring opening under these harsh conditions to form zwitterion iii via a push-pull mechanism, subsequently giving rise to a Grob-type fragmentation to afford 2-methyl-1-(diphenylmethylideneamino)propene iv, which was identified in the crude reaction mixture based on 1H NMR analysis (Scheme b).\textsuperscript{a,b,c,d}

**Scheme b**


\textsuperscript{b} Stevens, C.; Gallant, M.; De Kimpe, N. *Tetrahedron Lett.* 1999, 40, 3457-3460.


Section 3: NMR spectra of reported compounds

Br
\[
\begin{array}{c}
\text{COOMe} \\
\text{COOMe}
\end{array}
\]

6a (CDCl$_3$, 300 MHz)
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$\text{Br} \quad \text{COOEt} \quad \text{COOEt}$

**6c (CDCl$_3$, 300 MHz)**


Br

COOEt

COOEt

6c (CDCl₃, 75 MHz)
6d (CDCl$_3$, 300 MHz)
Chemical structure

$6d$ (CDCl$_3$, 75 MHz)
$\text{Cl} \quad \text{CN}
$ 

$6e \ (\text{CDCl}_3, \ 300 \text{ MHz})$
6e (CDCl₃, 75 MHz)
7a (CDCl₃, 300 MHz)
**7a (CDCl₃, 75 MHz)**
7b (CDCl₃, 300 MHz)
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[Image of a chemical structure labeled 7b (CDCl₃, 75 MHz)]
7c (CDCl₃, 300 MHz)
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$7d$ (CDCl$_3$, 300 MHz)
$7d$ (CDCl$_3$, 75 MHz)
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$\text{Ph} \text{N} \text{Ph}$

$8b$ (CDCl$_3$, 300 MHz)
8b (CDCl₃, 75 MHz)
9a (CDCl₃, 300 MHz)
\[ 9a \text{ (CDCl}_3, 75 \text{ MHz)} \]
9b (CDCl₃, 300 MHz)
9b (CDCl₃, 75 MHz)
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ii (CDCl$_3$, 75 MHz)
10a (CDCl₃, 300 MHz)
$10a$ (CDCl$_3$, 75 MHz)
$\textbf{10b (CDCl}_3, 300 \text{ MHz)}$
10b (CDCl$_3$, 75 MHz)