# New Ring Expansion of Cyclobutanones: Synthesis of Pyrrolinones, Pyrrolidines and Pyrroles

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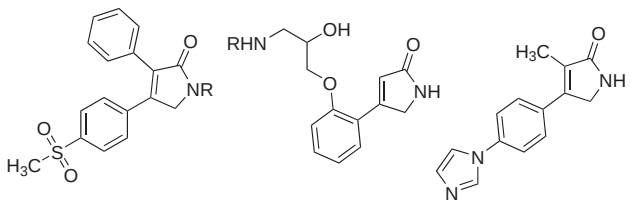
*Received 19 January 2004*

**Abstract:** 2,2-Dichlorocyclobutanones reacted with various amines to give ring opening leading to 4,4-dichlorobutanamides. These compounds proved to be suitable substrates for the synthesis of 3-pyrrolin-2-ones, 2-pyrrolidinones, pyrrolidines and pyrroles.

**Key words:** cyclobutanones, ring opening, ring expansion, pyrroles, heterocycles

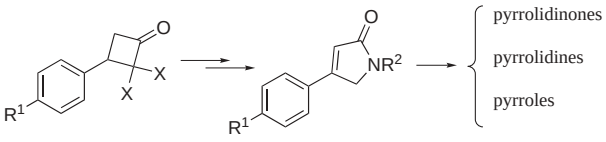
Cyclobutanones reveal interesting characteristics such as a high electrophilicity and ring tension which make them good substrates for ring transformation reactions.[1,2] Functionalized cyclobutanones have indeed been the subject of studies which describe their reactivity with nucleophiles to induce ring opening, ring contraction and ring expansion.[1–4] Various γ-butyrolactones and, to a smaller extent, some γ-lactams were synthesized via ring expansion of dihalocyclobutanones via Baeyer–Villiger[3] and Beckmann rearrangements or Schmidt reactions,[4] respectively. Reaction of dichlorocyclobutanones with azides,[4a–4c] Tamura's reagent [*O*-(methanesulfonyl)-hydroxylamine][4d,e] or its N-alkylated analogue[4f] resulted in various pyrrolidinones. Via these ring expansion methodologies, it would be possible to synthesize pyrrolidinones bearing leaving groups. These compounds could in turn give rise to pyrrolinones after elimination. However, no ring expansion of cyclobutanones was reported leading to the unsaturated 3-pyrrolin-2-ones, a class of compounds of particular importance as physiologically active compounds and as synthons for further transformation into various azaheterocycles. 3,4-Diarylpyrrolinones **1** were recently patented and show anti-inflammatory (R = alkyl) and cyclooxygenase-2 inhibitor (R = aryl) activities.[5] N-Unsubstituted pyrrolinones **2** are blood pressure reducing agents,[6] while 4-[4-(1*H*-imidazol-1-yl)phenyl]pyrrolinones **3** possess selective positive inotropic properties (Figure 1).[7]




**1a** (R = alkyl) **1b** (R = aryl) **2** (R = alkyl) **3**

**Figure 1**

The present paper describes the synthesis of 4-aryl-3-pyrrolin-2-ones from 3-aryl-2,2-dihalocyclobutanones via an amine-induced ring opening of the cyclobutanone ring and subsequent ring closure. Furthermore, these interesting compounds proved to be good substrates for further ring transformation into various five-membered azaheterocycles (Scheme 1). Ring opening of dihalocyclobutanones with amines has previously been described only with fused cyclobutanones like bicycloheptanes, -heptenes and benzocyclobutanones.[8] No monocyclic α,α-dichlorocyclobutanone was ever ring opened by amines.

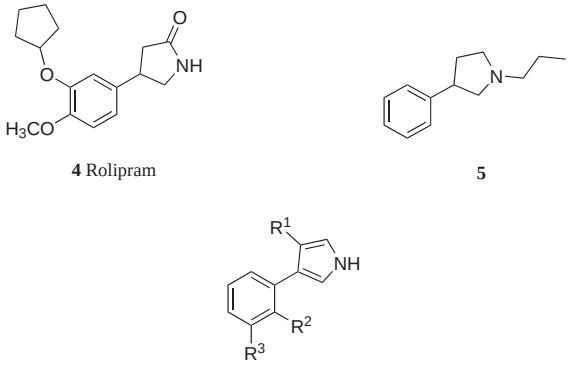



**Scheme 1**

Pyrrolidinones, pyrrolidines and pyrroles display a wide diversity of pharmacological and agrochemical activities and, accordingly, have received considerable attention in organic synthesis (Figure 2). Rolipram **4** is a well-known inhibitor of phosphodiesterase type IV, an anti-inflammatory agent and antidepressant.[9] Both enantiomers of this 3-aryl-2-pyrrolidinone are active. Several 3-aryl-1-propylpyrrolidines, e.g. **5**, show antagonistic effects towards dopaminergic autoreceptors and have a potential for treatment of central nervous system disorders.[10] The most important 3-arylpyrroles in agrochemistry are pyrrolnitrin **6a** and derivatives, which are used as antifungals (e.g. Beret® **6b**, Saphire® **6c**) and antimycobacterials (Figure 2).[11]

Both 2,2-dibromocyclobutanones and 2,2-dichlorocyclobutanones were synthesized in order to compare their ability for ring expansion towards 3-pyrrolinones. The synthesis of these small ring compounds involves a [2+2]-cycloaddition of in situ generated dihalogenated ketenes to substituted styrenes.[12,13] In contrast to the synthesis of 2,2-dibromocyclobutanone, which is a more laborious and low yielding procedure, 2,2-dichlorocyclobutanones are readily obtained from commercially

*SYNLETT* 2004, No. 6, pp 1059–1063
Advanced online publication: 01.04.2004
DOI: 10.1055/s-2004-822900; Art ID: G02304ST



**4** Rolipram

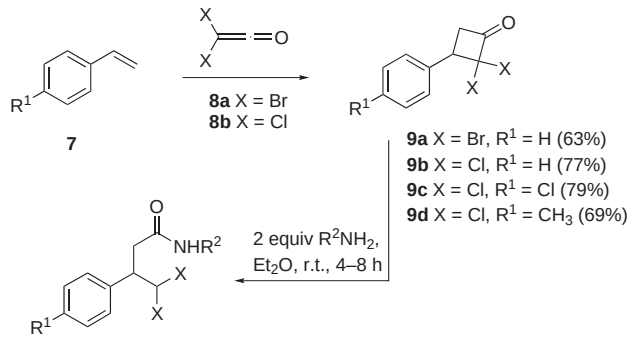
**5**

**6a** Pyrrolnitrin ($R^1 = R^3 = Cl$, $R^2 = NO_2$)
**6b** Beret® ($R^1 = CN$, $R^2 = R^3 = Cl$)
**6c** Saphire® ($R^1 = CN$, $R^2,R^3 = OCF_2O$)

**Figure 2**

available starting products. Both 2,2-dibromo-3-phenylcyclobutanone (**9a**; X = Br) and 2,2-dichloro-3-phenylcyclobutanone (**9b**; X = Cl) were treated with two equivalents of isopropylamine to induce ring opening towards 3-aryl-4,4-dihalo-*N*-isopropylbutanamides (**10a**,**b**; Scheme 2).

When fewer equivalents of amine were used, longer reaction times were required and, as a consequence, more side products were formed which hamper the recrystallization of the butanamides **10**. The reaction of cyclobutanone **9b** with aniline did not result in a ring opening even when applying higher temperatures or more polar solvents like MeCN or DMSO. The ring opening of 3-phenyl-2,2-dichlorocyclobutanone (**9b**) with isopropylamine proceeded in much higher yield as compared with 3-phenyl-2,2-dibromocyclobutanone (**9a**).



**7**

**8a** X = Br
**8b** X = Cl

**9a** X = Br, $R^1$ = H (63%)
**9b** X = Cl, $R^1$ = H (77%)
**9c** X = Cl, $R^1$ = Cl (79%)
**9d** X = Cl, $R^1$ = $CH_3$ (69%)

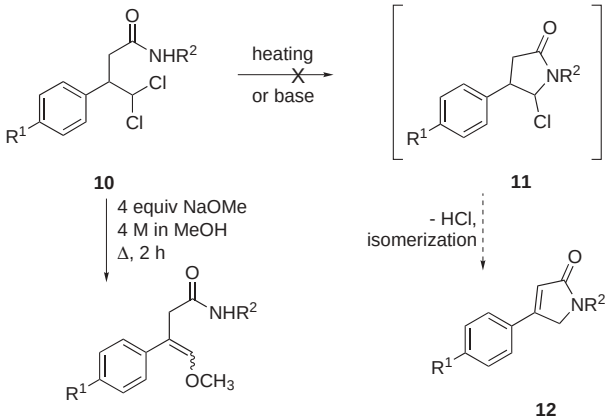
2 equiv $R^2NH_2$, $Et_2O$, r.t., 4–8 h

**10a** X = Br, $R^1$ = H, $R^2$ = *i*-Pr (52%)
**10b** X = Cl, $R^1$ = H, $R^2$ = *i*-Pr (70%)
**10c** X = Cl, $R^1$ = Cl, $R^2$ = *i*-Pr (56%)
**10d** X = Cl, $R^1$ = $CH_3$, $R^2$ = *i*-Pr (62%)
**10e** X = Cl, $R^1$ = H, $R^2$ = Pr (72%)
**10f** X = Cl, $R^1$ = H, $R^2$ = *c*-Hex (64%)
**10g** X = Cl, $R^1$ = H, $R^2$ = Bn (58%)

**Scheme 2**

Because of the difficult synthesis of dibromocyclobutanone **9a** and the low yield of the ring opening product **10a**, further elaboration towards various 3-pyrrolin-2-one derivatives was carried out with dichlorocyclobutanones **9b**–**d** as starting materials. In that way, various new 3-aryl-4,4-dichlorobutanamides **10b**–**g** were synthesized from the corresponding cyclobutanones **9** in good yield (Scheme 1).

Attempts to cyclize dichlorobutanamides **10** directly to pyrrolinones by heating in toluene or DMSO yielded only traces of pyrrolinone **12** after reflux for 15 hours (Scheme 2). Also heating in aqueous 2 M HCl did not improve the yield. When *t*-BuOK was used as a base no cyclization occurred, probably because the CH of the $CHCl_2$-moiety is more acidic than the NH of the amide, resulting in side reactions. However, reaction of dichlorobutanamide **10b** with 2 equivalents of 2 M NaOMe in methanol at reflux temperature for 2 hours yielded a mixture of compounds, among others *N*-isopropyl-4-methoxy-3-phenyl-3-butenamide (**13a**; a mixture of the *E*- and *Z*-isomer in a ratio 72:28). This enol ether was thought to be a good substrate for ring closure towards pyrrolin-2-ones and therefore, the reaction was optimized to yield a maximum amount of compound **13a**. After careful evaluation of the reaction with various equivalents of NaOMe, different concentrations, reaction times and temperatures, a selective reaction towards **13a** was accomplished with 4 equivalents of 4 M sodium methoxide in methanol at reflux temperature for 2 hours. In this way, several enol ether derivatives **13** were synthesized in 82–97% yield (Scheme 3). The obtained crystalline *N*-alkyl-4-methoxy-3-phenyl-3-butenamides (**13**) occurred in both the *E*- and *Z*-isomers in ratios varying from 74:26 to 88:12. The major *E*-isomer could be separated from the mixture by column chromatography, whereas the *Z*-minor isomer could not be obtained as a pure isomer.



**10**

4 equiv NaOMe
4 M in MeOH
Δ, 2 h

**11**

- HCl,
isomerization

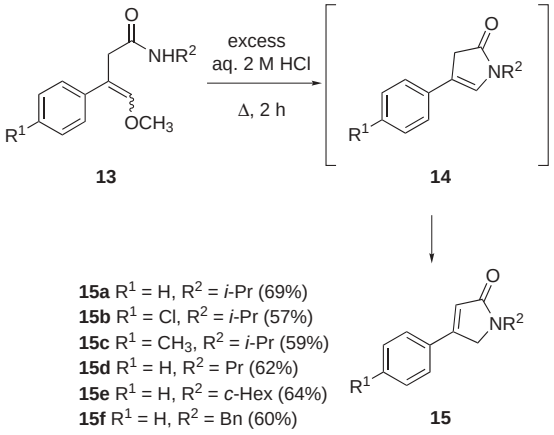
**12**

**13a** $R^1$ = H, $R^2$ = *i*-Pr (91%) (*E*/*Z* 88/12)
**13b** $R^1$ = Cl, $R^2$ = *i*-Pr (97%) (*E*/*Z* 75/25)
**13c** $R^1$ = $CH_3$, $R^2$ = *i*-Pr (93%) (*E*/*Z* 86/14)
**13d** $R^1$ = H, $R^2$ = Pr (96%) (*E*/*Z* 78/22)
**13e** $R^1$ = H, $R^2$ = *c*-Hex (96%) (*E*/*Z* 75/25)
**13f** $R^1$ = H, $R^2$ = Bn (82%) (*E*/*Z* 74/26)

**Scheme 3**

To accomplish a ring closure of 4-methoxy-3-butenamides **13**, the mixture of both stereoisomers of the enol ethers were treated with an excess of aqueous 2 M HCl. After protonation of the enol ether moiety, a nucleophilic

attack of the amide and subsequent elimination of methoxide resulted in 4-pyrrolin-2-ones **14**, which isomerized spontaneously to the thermodynamically more stable 3-pyrrolin-2-ones **15**. The value of this reaction pathway is reflected in the fact that both previous steps (**9** to **10** and **10** to **13**) proceed in high yield and that in fact no purification is needed before the ring closure reaction. With this new ring expansion procedure, several 3-pyrrolin-2-ones **15** were synthesized which offer good perspectives for further ring transformations to physiologically interesting pyrrolidinones, pyrrolidines and pyrroles (Scheme 4).



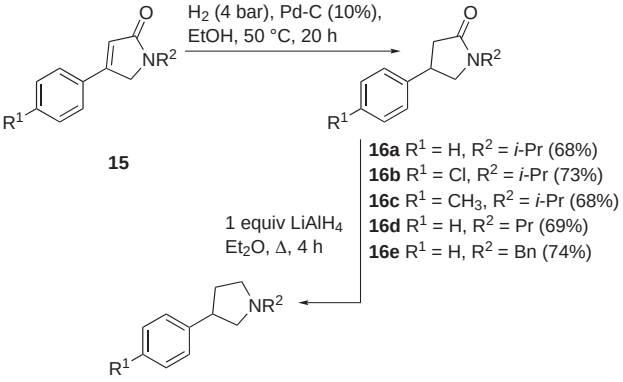

**Scheme 4**

As stated in the introduction, this is the first ring expansion of cyclobutanones towards 3-pyrrolin-2-ones, which are suitable synthons for further synthesis, and which show important physiological activities.[5–7]

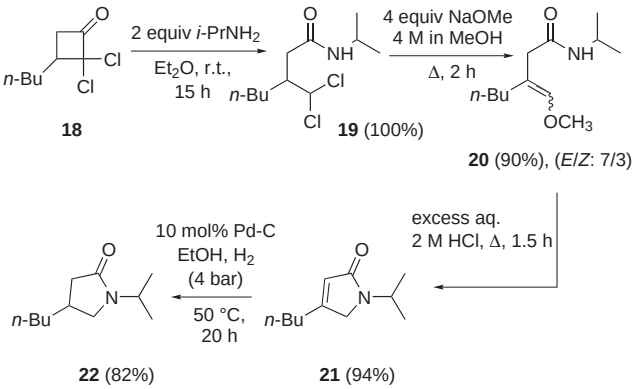
1-Alkyl-4-aryl-3-pyrrolin-2-ones (**15**) were reduced with hydrogen on palladium towards the saturated pyrrolidinones **16** in good yield. Further reduction of pyrrolidinones **16** with $LiAlH_4$ in diethyl ether under reflux for 4 hours resulted in 3-arylpyrrolidines **17** in 63–76% yield (Scheme 5). Both classes of compounds have been shown to possess promising activities from a pharmaceutical and agrochemical point of view. The novel synthetic pathway presented here can be performed on a multigram scale and provides various types of easily available five membered azaheterocycles.

To expand the scope of the ring expansion, effords were done to perform the reaction sequence with alkylcyclobutanones (Scheme 6). Ring opening of 3-butyl-2,2-dichlorocyclobutanone[14] (**18**) with isopropylamine yielded butanamide **19** in quantitative yield. Reaction of **19** with sodium methoxide resulted in enol ether **20** which could be cyclized by treatment with aqueous HCl. The obtained 4-butyl-3-pyrrolin-2-one (**21**) was reduced to pyrrolidinone **22**. These high yielding reactions underline the value of the conversion of cyclobutanones into pyrrolinones and related heterocycles (Scheme 6).

The recently disclosed method to convert 3- and 4-pyrrolin-2-ones into pyrroles by the use of 9-borabicyc-




**Scheme 5**




**Scheme 6**

lo[3.3.1]nonane (9-BBN) was applied here to reduce 3-pyrrolinones **15** to the corresponding 3-arylpyrroles **23**.[15] It should be underlined that reaction of **15** with other hydride sources, e.g. $LiAlH_4$, $NaBH_4$ or $BH_3$ did not yield pyrroles at all. The best yields were obtained when pyrrolinones **15** were treated with 3 equivalents of 9-BBN in toluene at reflux for 15 hours. This procedure provided several new 1-alkyl-3-arylpyrroles **23**, a class of compounds which exhibit a wide range of agrochemical and pharmacological properties (Scheme 7).

In summary, a new ring expansion of 3-aryl-2,2-dihalocyclobutanones was developed towards 3-pyrrolin-2-ones in three high yielding steps. These heterocycles are of particular importance due to their physiological properties and their versatile reactivity. Selective reductions led to 3-arylpyrrolidinones, pyrrolidines and pyrroles. This synthetic protocol provides an easy and good yielding synthesis of various interesting azaheterocyclic compounds.

**4,4-Dichloro-*N*-isopropyl-3-phenylbutanamide (10b)**. To a solution of 5.00 g (23.25 mmol) 2,2-dichloro-3-phenylcyclobutanone (**9b**) in 50 mL of $Et_2O$ was added a solution of 2.74 g (46.51 mmol, 2 equiv) isopropylamine in 50 mL of $Et_2O$ at 0 °C during 15 min.

After addition, cooling was stopped and the reaction mixture was stirred at r.t. for 8 h. The resulting mixture was poored into 100 mL of aq 0.5 M NaOH and extracted with $Et_2O$ (3 × 100 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated in vacuo yielding 4,4-dichloro-*N*-isopropyl-3-phenylbutanamide (**10b**) as a brown solid. Recrystallization ($Et_2O$–hexane–$CH_2Cl_2$, 5:1:5); yield 70%, mp 97–98 °C. $^1$H NMR ($CDCl_3$): δ = 0.91 and 1.07 (2 × d, *J* = 6.6 Hz, 6 H), 2.65 and 2.93 (2 × dd, *J* = 14.5 Hz, 8.6 Hz and 5.9 Hz, 2 H), 3.85–3.94 (m, 1 H), 3.94 (sept, *J* = 6.6 Hz, 1 H), 5.25 [(s (b), 1 H], 6.07 (d, *J* = 4.6 Hz, 1 H), 7.27–7.38 (m, 5 H). $^{13}$C NMR ($CDCl_3$): δ = 2 × 22.5, 38.4, 41.4, 52.2, 76.3, 128.0, 2 × 128.4, 2 × 129.0, 137.6, 169.0. IR (KBr): 3342, 1647, 1535 cm$^{-1}$. MS: *m/z* (%) = no M$^+$, 238/240 (12), 202 (100), 115 (15), 101 (18), 86 (48), 69 (42).

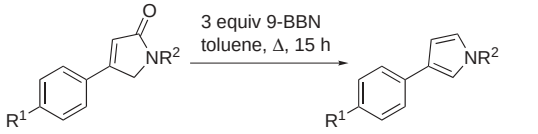
**(*E*)-*N*-Isopropyl-4-methoxy-3-phenyl-3-butenamide (13a)**. To 1.10 g (4.01 mmol) of butanamide **10b** was added 4.0 mL of 4 M NaOMe in MeOH. After 2 h of reflux, the mixture was poored into $H_2O$ and extracted three times with $CH_2Cl_2$. Drying of the extract ($MgSO_4$), filtration and evaporation of the solvent resulted in butenamide **13a** as a dark brown solid (*E*/*Z* 88:12, yield 0.85 g, 91%), which could be easily recrystallized from EtOAc or chromatographed on column to yield the pure *E*-isomer (hexane–EtOAc, 1:1, $R_f$ = 0.35); yield 0.56 g (60%), mp 106–108 °C. $^1$H NMR ($CDCl_3$): δ = 1.04 (d, *J* = 6.6 Hz, 6 H), 3.38 (s, 2 H), 3.78 (s, 3 H), 4.02 (sept, *J* = 6.6 Hz, 1 H), 5.70 [s (b), 1 H], 6.59 (s, 1 H), 7.26–7.32 (m, 5 H). $^{13}$C NMR ($CDCl_3$): δ = 2 × 22.6, 36.2, 41.2, 60.2, 113.9, 2 × 125.2, 126.5, 2 × 128.7, 138.4, 147.3, 170.1. IR (KBr): 3380, 1675, 1520 cm$^{-1}$. MS: *m/z* (%) = 233 (62) [M$^+$], 148 (100), 147 (35), 117 (35), 43 (60).

**1-Isopropyl-4-phenyl-3-pyrrolin-2-one (15a)**. To 2.00 g (8.6 mmol) of **13a** was added an excess (25 mL) of an aq 2 M HCl solution. The suspension was refluxed for 2 h. After cooling, the acidic mixture was three times extracted with $CH_2Cl_2$. Drying of the extract ($MgSO_4$) and evaporation of the solvent resulted in 1.60 g of crystalline pyrrolin-2-one **15a**. Purification was performed with column chromatography (EtOAc–hexane, 1:1, $R_f$ = 0.17); yield 1.20 g (69%), mp 75–77 °C (no literature data). $^1$H NMR, $^{13}$C NMR and MS spectroscopic data were in accordance with literature data (IR spectroscopic data were not reported).[16] IR (KBr): 1655, 1462 cm$^{-1}$. (**15e**,**f**: known compounds).[17]

**1-Isopropyl-4-phenylpyrrolidin-2-one (16a)**. A solution of 0.93 g (4.6 mmol) of 3-pyrrolin-2-one **15a** and 0.10 g (ca. 10%) of palladium on carbon in 10 mL of dry MeOH, was stirred under $H_2$ atmosphere (4 bar) at 50 °C for 20 h. After filtration over Celite®, the solvent was removed by evaporation in vacuo, leaving 0.70 g of pyrrolidinone **16a**. A purification by Kugelrohr destillation (bp 108–112 °C/0.15 mmHg) yielded 0.64 g (68%) of pure product. $^1$H NMR ($CDCl_3$): δ = 1.15 (d, *J* = 7.3 Hz, 3 H), 1.17 (d, *J* = 7.3 Hz, 3 H), 2.57 and 2.82 (2 × dd, *J* = 16.8 Hz, 8.9 Hz and 8.3 Hz, 2 H), 3.31 and 3.73 (2 × dd, *J* = 9.5 Hz, 8.1 Hz and 7.9 Hz, 2 H), 3.53 (m, 1 H), 4.45 (m, 1 H), 7.21–7.37 (m, 5 H). $^{13}$C NMR ($CDCl_3$): δ = 19.7, 19.9, 37.3, 39.5, 42.5, 49.2, 2 × 126.7, 127.0, 2 × 128.9, 142.7, 173.0. IR (NaCl): 1675, 1601, 1489 cm$^{-1}$. MS: *m/z* (%) = 203 (46) [M$^+$], 189 (23), 188 (100), 117 (25), 104 (74), 91 (31), 56 (25), 43 (25). (**16d**,**e**: known compounds)[18,19]

**1-Isopropyl-3-phenylpyrrolidine (17a)**. Pyrrolidin-2-one **16a** (0.10 g, 0.49 mmol) was dissolved in 5 mL of dry diethyl ether. To this mixture 0.02 g (0.52 mmol; 1.05 equiv) $LiAlH_4$ was added at 0 °C. After the addition, the mixture was refluxed for 4 hours and subsequently quenched with ice-water. Extraction with 3 × 5 mL of $Et_2O$ and drying of the extract ($MgSO_4$) yielded 0.08 g of pyrrolidine **17a** after removal of the solvent. Purification was performed with column chromatography ($CH_2Cl_2$–MeOH–$Et_3N$, 90:9:1, $R_f$ = 0.28); yield 0.07 g (76%). $^1$H NMR ($CDCl_3$): δ = 1.14 (d, *J* = 6.3 Hz, 3 H), 1.15 (d, *J* = 6.3 Hz, 3 H), 1.84–1.97 (m, 1 H), 2.26–2.40 (m, 1 H), 2.47 (m, 1 H), 2.48 and 3.25 (2 × dd, *J* = 9.2 Hz, 8.9 Hz and 8.3 Hz, 2 H), 2.67 and 3.02 (2 × dt, *J* = 9.2 Hz, 7.9 Hz and 6.2 Hz, 2 H), 3.39 (quint, *J* = 8.6 Hz, 1 H), 7.17–7.33 (m, 5 H). $^{13}$C NMR ($CDCl_3$): δ = 21.4, 21.5, 32.9, 43.5, 52.3, 55.2, 59.9, 126.3, 2 × 127.3, 2 × 128.4, 144.4. IR (NaCl): 1605, 1498, 1457 cm$^{-1}$. MS: *m/z* (%) = 189 (M$^+$, 9), 175 (13), 174 (100), 131 (20), 91 (15), 56 (15), 43 (35). (**17d**,**e**: known compounds)[20,21]

**1-Isopropyl-3-phenylpyrrole (23a)**. To a solution of 1.00 g (5.00 mmol) 3-pyrrolin-2-one **15a** in 5 mL of dry toluene was added 3 equiv (1.80 g, 15.00 mmol) of 9-borabicyclo[3.3.1]nonane as a solid dimer. The mixture was refluxed for 15 h and subsequently poured in 25 mL of $H_2O$. Extraction with $Et_2O$ (3 × 25 mL), drying ($MgSO_4$) and evaporation of the solvents in vacuo afforded pyrrole **23a**, which was purified by column chromatography (EtOAc–hexane, 95:5 $R_f$ = 0.25); yield 0.37 g (40%). $^1$H NMR ($CDCl_3$): δ = 1.47 (d, *J* = 6.6 Hz, 6 H), 4.23 (sept, *J* = 6.6 Hz, 1 H), 6.44 (dd, *J* = 2.8 Hz and 2.0 Hz, 1 H), 6.73 (dd, 2.8 Hz and 2.3 Hz, 1 H), 7.02 (dd, *J* = 2.3 Hz and 2.0 Hz, 1 H), 7.10–7.16 (m, 1 H), 7.28–7.33 (m, 2 H), 7.49–7.52 (m, 2 H). $^{13}$C NMR ($CDCl_3$): δ = 2 × 23.9, 51.0, 105.7, 115.1, 119.2, 2 × 124.9, 125.1, 2 × 128.5, 130.9, 136.1. IR (NaCl): 1602, 1545, 1483 cm$^{-1}$. MS: *m/z* (%) = 185 (100) [M$^+$], 170 (84), 143 (81), 115 (46), 105 (32), 43 (21). (**23d**,**e**: known compounds)[22,23]




**15**

**23a** $R^1$ = H, $R^2$ = *i*-Pr (40%)
**23b** $R^1$ = Cl, $R^2$ = *i*-Pr (51%)
**23c** $R^1$ = $CH_3$, $R^2$ = *i*-Pr (52%)
**23d** $R^1$ = H, $R^2$ = *c*-Hex (56%)
**23e** $R^1$ = H, $R^2$ = Bn (61%)

**Scheme 7**

## Acknowledgment

The authors are indebted to the IWT (Flemish Institute for the Promotion of Scientific-Technological Research in Industry), the FWO-Flanders and Ghent University (GOA) for financial support.

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