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Synthesis of azacycloalkane-1,2-fused pyrroles *via* alkylation of cyclic ketimines with α-bromo ketones

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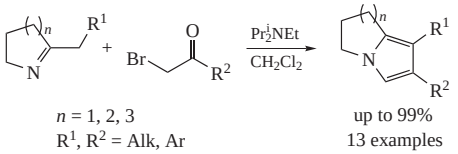
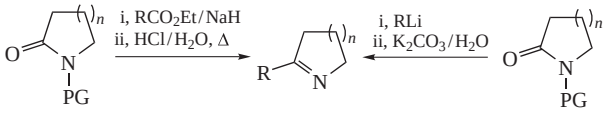
The reaction of 2-alkyl-substituted 5-, 6- and 7-membered cyclic imines with α-bromo ketones in the presence of Hünig's base affords 2,3-dihydro-1*H*-pyrrolizines, 5,6,7,8-tetrahydroindolizines and 6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepines, respectively.



2-Substituted cyclic ketimines can be used as building blocks for incorporation of fragment of cyclic amine[1] or aminoalkyl group[2] thus opening access to biologically active compounds and analogues of natural products.[3] Herein, we studied the reaction of cyclic imines with α-bromo ketones. We anticipated that such reactions should bring about fused pyrrole compounds. Some cases of alkylation of 6-membered cyclic imines to annulated aromatic systems were reported.[4] The synthesis of lamellarin alkaloids of fused pyrrole type and their hybrids attracted much attention as well.[5] 5-Membered imines bearing benzyl group at 2-position were used for preparing biologically active dihydropyrrolizines.[6] We decided to investigate such processes more thoroughly.

Starting 5-, 6- and 7-membered ketimines can be prepared by the Claisen condensation of N-protected lactams with esters followed by acidic hydrolysis, decarboxylation and recyclization to form target cyclic imines. An alternative direct route is the reaction of organometallic compounds with N-protected lactams (Scheme 1).[7]



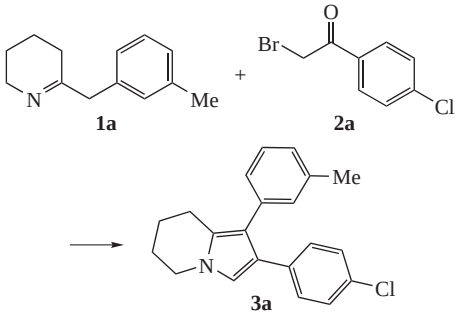
Scheme 1

To find optimal reaction conditions, a model reaction of 2-(3-methylbenzyl)piperideine **1a** and α-bromo-*p*-chloroacetophenone **2a** was investigated (Scheme 2, Table 1). First, an effect of base was studied. When carbonates (K_2CO_3, $NaHCO_3$) in DMF, EtOH or MeCN were used, the yields of product **3a** did not exceed 36% for all these systems (entries 1–3). In case of more basic sodium hydride nothing of **3a** was formed (entry 4). Luckily, the application of triethylamine and *N*,*N*-diisopropylethylamine (Hünig's base) in dichloromethane provided good yields of the target compound **3a** (72 and 84%). Therefore, Pr^i_2NEt was the base of choice (entry 6). The further screening of solvents (THF, diethyl ether, toluene, DMSO, DMF, dioxane, dichloroethane, MeCN) and varying the amount of the base and bromo ketone **2a** did not lead to any improvements. Most probably, Pr^i_2NEt possessing low nucleophilicity would minimize its side alkylation with bromo ketone.

Table 1 Screening of conditions for model annulation of cyclic imine **1a**.[a]

Entry	Solvent	Base	Yield of **3a** (%)
1	EtOH	$NaHCO_3$	17
2	DMF	K_2CO_3	36
3	MeCN	K_2CO_3	27
4	DMF	NaH	–
5	CH_2Cl_2	Et_3N (1.2 equiv.)	72
6	CH_2Cl_2	Pr^i_2EtN (1.2 equiv.)	84

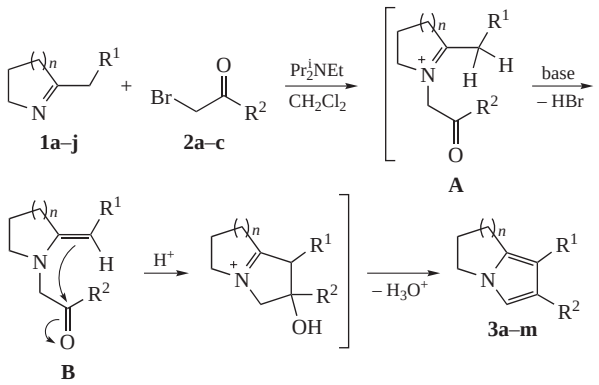
[a]With 1.3 equiv. of **2a** in all cases.



Scheme 2 For conditions, see Table 1.

To evaluate scope and limitation of the method, we tested various 5, 6 and 7-membered ketimines bearing different substituents at 2-position (Scheme 3).† The reaction of α-bromo-*p*-chloroacetophenone **2a** with six-membered imines **1a**–**e** produced corresponding pyrroles **3a**–**e** in up to 99% yield. Bromo ketones **2b**,**c** were also good substrates to form pyrroles **3f**–**h** in good yields. As a rule very high yields were achieved for any benzyl-substituted imines without significant influence of the substituents in aryl fragment. However, lower yield (50%) was observed in

† *General procedure for preparation of pyrroles* **3a**–**m**. An appropriate bromo ketone **2** (1.25 mmol) and *N*,*N*-diisopropylethylamine (0.1 ml, 0.058 mmol) were added to a solution of an appropriate cyclic imine **1**[7] (0.50 mmol) in CH_2Cl_2 (5 ml) at room temperature. The reaction mixture was kept at room temperature for 2 days. Then the volatiles were evaporated and product **3** was purified by column chromatography (hexane/CH_2Cl_2).



Imine	*n*	R^1	Bromo ketone	R^2	Product	Yield (%)
1a	2	3-MeC_6H_4	**2a**	4-ClC_6H_4	**3a**	84
1b	2	4-FC_6H_4	**2a**	4-ClC_6H_4	**3b**	99
1c	2	3,4-$(MeO)_2C_6H_3$	**2a**	4-ClC_6H_4	**3c**	95
1d	2	4-MeC_6H_4	**2a**	4-ClC_6H_4	**3d**	88
1e	2	Pr	**2a**	4-ClC_6H_4	**3e**	50
1b	2	4-FC_6H_4	**2b**	Ph	**3f**	77
1a	2	3-MeC_6H_4	**2c**	Bu^t	**3g**	51
1b	2	4-FC_6H_4	**2c**	Bu^t	**3h**	52
1f	1	2-MeC_6H_4	**2a**	4-ClC_6H_4	**3i**	43
1g	1	3-ClC_6H_4	**2a**	4-ClC_6H_4	**3j**	75
1g	1	3-ClC_6H_4	**2b**	Ph	**3k**	27
1h	1	Pr	**2a**	4-ClC_6H_4	–	traces
1i	3	Ph	**2a**	4-ClC_6H_4	**3l**	56
1j	3	Pr	**2a**	4-ClC_6H_4	**3m**	21

Scheme 3

the case of butyl-substituted imine **1e**. 5-Membered imines **1f**–**g** gave the desired pyrroles **3i**–**k** in 27–75% yields. Lower yields for this series can be explained by significant strain of formed molecules containing 5-membered pyrrollidine ring fused with pyrrole. 2-Butylpyrroline **1h** formed only trace amounts of the target pyrrole. 7-Membered imines **1i**,**j** can also enter in the annulation to give corresponding pyrroles **3l**,**m** in 21–56% yields. It is of note that some of the prepared compounds were poorly stable, for example 7-membered derivatives **3l**,**m** and 3-alkyl-substituted pyrrole **3e** decomposed during attempted purification on silica gel.

The observed results are in good agreement with the reaction mechanism shown in Scheme 3. Alkylation of ketimines with bromo ketones resulted in formation of iminium salts **A** transformed to the corresponding keto enamines **B**. Subsequent cyclization and water elimination gave finally the target pyrroles. In the case of enamines bearing additional aryl group (R^1 = Ar) the reaction is facilitated due to the formation of more stable intermediate.

In conclusion, the reaction of 5–7-membered cyclic ketimines with α-bromo ketones was studied. The influence of ring size and substituent in α-ketimines was revealed. The procedure developed can be expediently used for the synthesis of pyrroles fused with saturated azacycloalkane ring.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.05.013.

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*2-(4-Chlorophenyl)-1-(*m*-tolyl)-5,6,7,8-tetrahydroindolizine* **3a**: yield 135 mg (84%), yellowish solid, mp 106–109 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.82–1.88 (m, 1H, CH_2), 2.00–2.06 (m, 2H, CH_2), 2.34 (s, 3H, Me), 2.84 (t, 2H, CH_2, *J* 6.35 Hz), 4.04 (t, 2H, CH_2, *J* 6.07 Hz), 6.74 (s, 1H, Ar), 6.99 (d, 1H, Ar, *J* 7.54 Hz), 7.05 (br. s, 2H, Ar), 7.13–7.23 (m, 5H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.1, 21.5, 22.8, 23.5, 45.5, 117.5 (Ar), 118.0 (Ar, C_q), 122.1 (Ar, C_q), 126.2 (Ar), 127.2 (Ar), 127.8 (Ar, C_q), 127.9 (Ar), 128.1 (Ar), 129.2 (Ar), 130.6 (Ar), 130.7 (Ar, C_q), 134.5 (Ar, C_q), 135.5 (Ar, C_q), 137.4 (Ar, C_q). HRMS (ESI), *m*/*z*: 322.1363 $[M+H]^+$ (calc. for $C_{21}H_{21}ClN^+$, *m*/*z*: 322.1358).

*7-(3-Chlorophenyl)-6-(4-chlorophenyl)-2,3-dihydro-1*H*-pyrrolizine* **3j**: yield 123 mg (75%), yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.54–2.63 (m, 2H, CH_2), 3.02 (t, 2H, CH_2, *J* 7.33 Hz), 4.04–4.08 (m, 2H, CH_2), 6.78 (s, 1H, Ar), 7.07–7.10 (m, 1H, Ar), 7.16–7.29 (m, 7H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.5, 27.3, 46.6, 112.5 (Ar, C_q), 113.4 (Ar), 125.0 (Ar), 126.2 (Ar, C_q), 126.8 (Ar), 128.1 (Ar), 128.3 (Ar), 129.3 (Ar), 129.5 (Ar), 131.3 (Ar, C_q), 133.9 (Ar, C_q), 134.6 (Ar, C_q), 136.8 (Ar, C_q), 138.1 (Ar, C_q). HRMS (ESI), *m*/*z*: 328.0661 $[M+H]^+$ (calc. for $C_{19}H_{16}Cl_2N^+$, *m*/*z*: 328.0655).

*2-(4-Chlorophenyl)-1-phenyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]-azepine* **3l**: yield 90 mg (56%), dark oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.72 (br. s, 2H, CH_2), 1.88 (br. s, 4H, CH_2), 2.77 (br. s, 2H, CH_2), 4.03 (br. s, 2H, CH_2), 6.74 (s, 1H, Ar), 7.08–7.10 (m, 2H, Ar), 7.17–7.22 (m, 4H, Ar), 7.26–7.30 (m, 1H, Ar), 7.34–7.38 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4, 27.9, 29.7, 31.0, 50.5, 118.9 (Ar), 120.2 (Ar, C_q), 120.5 (Ar, C_q), 125.7 (Ar), 128.0 (Ar), 129.0 (Ar), 130.5 (Ar, C_q), 130.7 (Ar), 133.6 (Ar, C_q), 134.5 (Ar, C_q), 136.2 (Ar, C_q). HRMS (ESI), *m*/*z*: 322.1347 $[M+H]^+$ (calc. for $C_{21}H_{21}ClN^+$, *m*/*z*: 322.1358).

For more information, see Online Supplementary Materials.