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Efficient Synthesis of Pharmaceutically Relevant Prochiral Heterocyclic Aminoketones

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Abstract

In this work, we report a practical method for alkylation of saturated heterocycles with chloroacetone yielding prochiral heterocyclic ketones, including previously not described molecules. The desired building blocks were obtained with high yields in hydrochloric salt forms, without the need for chromatographic purification.

Keywords

prochiral aminoketones, saturated amine heterocycles, chloroacetone, alkylation, selective precipitation

1 Introduction

Prochiral aminoketones bearing different saturated heterocycles represent an important group of building blocks that can be utilized for the synthesis of active pharmaceutical ingredients containing (optically active) polyamines (such as selective P2X3 receptor antagonist RO-85 for inflammatory pain (**1**) [1], potential anticancer agent LPA2 (EDG4) antagonists [2], anti-inflammatory Cancer Osaka thyroid (COT) kinase inhibitors [3], potential antimalarial 4-aminoquinoline derivatives [4]), amino alcohols (such as analgesic 5-HT receptor agonists (**2**) [5]) and oximes (e.g. potential antibacterial agent **3** [6]) (Fig. 1).

Based on literature, a variety of reactions can be employed for the synthesis of the saturated heterocyclic aminoketones (Fig. 2), such as Grignard-type substitution (**I**) [7], intermolecular α-carbonyl carbene insertion (**II**) [8], alkylation with chloroacetone (**III**) [9], Rabe amination (**IV**) [10], alcohol amination (**V**) [11] and multicomponent alkylation (**VI**) [12]. However, most of them require expensive catalysts (Ru-complex, $CuNiAlO_x$ or $Ru_3(CO)_{12}$), inert atmosphere, elevated temperatures (up to 150 °C) or operate with lower yields (20–37%) and long reaction times (20–24 h).

Herein we describe a rapid and catalyst-free method for the synthesis of different aminoketones starting from the respective saturated heterocycles.

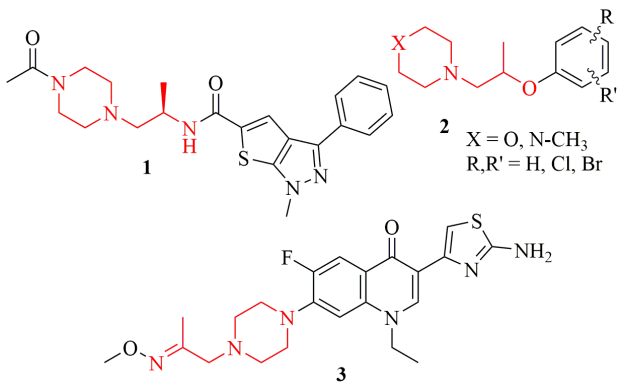

Fig. 1 API candidates

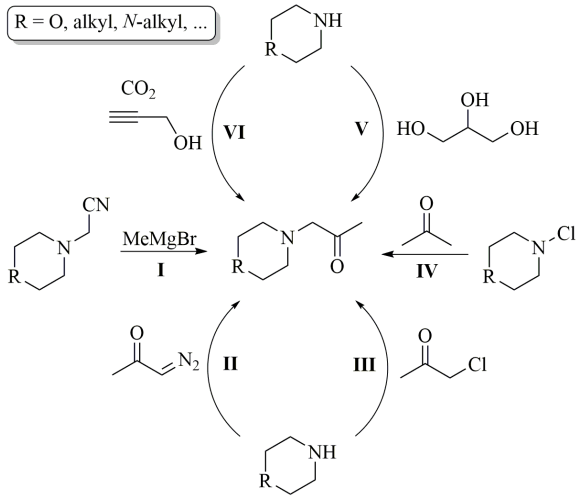

Fig. 2 Published syntheses of saturated heterocyclic aminoketones

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2 Results and discussion

For the synthesis of the aminoketones, the alkylation approach of the corresponding saturated amine heterocycle with chloroacetone (**5**) was chosen (Fig. 2, Method **III**). The commercially available morpholine (**4a**) proved to be suitable as a model compound for the optimization. At the start, the method widely used previously by our research group for the synthesis of various acetone-derivatives was employed. Although this method published by Martínez-Peragón et al. [13] provided full conversion within 4.5 hours, it required chromatographic purification.

However, column chromatography is often challenging when purifying basic compounds due to the ionic interactions with ionized silanol groups of silica gel [14]. Furthermore, as the target compounds are non-UV-active, the process cannot be directly followed by a UV detector and requires staining for visualization. Thus, an alternative work-up of the reaction mixture was introduced: by adjusting the pH of the aqueous phase, amines can be extracted with an organic solvent (usually, EtOAc, DCM). However, in the case of morpholine (**4a**) only quite moderate isolated yield of the alkylation product (**6a**) could be achieved due to its high solubility in the aqueous phase either under acidic or basic conditions (Table 1, Entry 1). Since both the starting material and the product are soluble in water, a work-up excluding this solvent was necessary. Acetone was replaced with non-miscible low-boiling point solvent methyl *tert*-butyl ether (MTBE) (Table 1, Entries 2–4).

For the synthesis of **6a**, two methodologies were developed (Fig. 3 and Table 1). The first method (Method A) used potassium carbonate (K_2CO_3) as external base. Similar to the process in acetone, K_2CO_3 is not soluble in MTBE

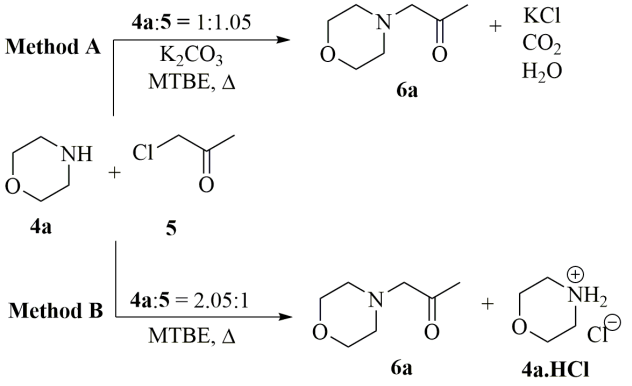
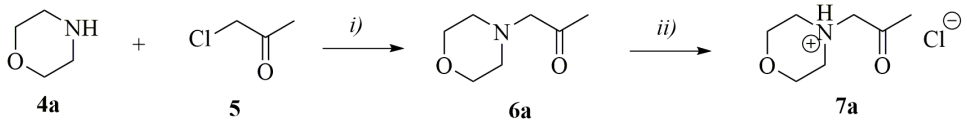


Fig. 3 Methods for alkylation of morpholine (**4a**) with chloroacetone (**5**)

which simplifies the work-up procedure as all inorganic byproducts can be removed by filtration. As the amine heterocycles generally have a pK_a value around 9–11 (in case of **6a** pK_a = 9.0), the second method (Method B) applied morpholine (**4a**) in 2-fold excess to chloroacetone (**5**) also as base to capture the forming hydrochloric acid. Moreover, in case of Method B the forming **4a.HCl** readily precipitates from the solution, further simplifying the composition of the reaction mixture.

In the reaction of two equivalents of **4a** with **5** at room temperature, full conversion could not be reached even after 48 h (Table 1, Entry 3), in contrast to the reaction under reflux which completed in 8 h (Table 1, Entry 4). While the reaction employing two equivalents of **4a** for **5** resulted in quantitative yield (Table 1, Entry 4), the use of one equivalents of **4a** for **5** in the presence of K_2CO_3 as external base led to considerably lower yield, although TLC indicated full conversion (Table 1, Entry 2: Method A). The reason for the decreased yield can be explained by inspection of the filter cake's composition. It was confirmed by low-field benchtop NMR (Fig. 4) that the solid from the reaction

Table 1 Optimization of the alkylation of morpholine (**4a**) with chloroacetone (**5**)



Entry	Method	i)						ii)
	Solvent	**5** (equiv.)	External base	Base (equiv.)	Temperature	Reaction time (h)	**6a** yielda (%)	**7a** yielda (%)
1	Acetone	1.1	K_2CO_3	1.5	reflux	4.5	34	-
2 **A**	MTBE	1.1	K_2CO_3	1.5	reflux	12	78	56
3	MTBE	0.5	-	-	r.t.	48	75	-
4 **B**	MTBE	0.5	-	-	reflux	8	100	99

[a] Reaction conditions: *i*) morpholine **4a** (1000 μL) in 10 mL solvent, 1.1 or 0.5 equiv. of **5** and 1.5 equiv. K_2CO_3 if indicated, temperature as indicated. *ii*) 1.05 equiv. of HCl in dioxane (For experimental procedures and analytical characterization see Supplement.)

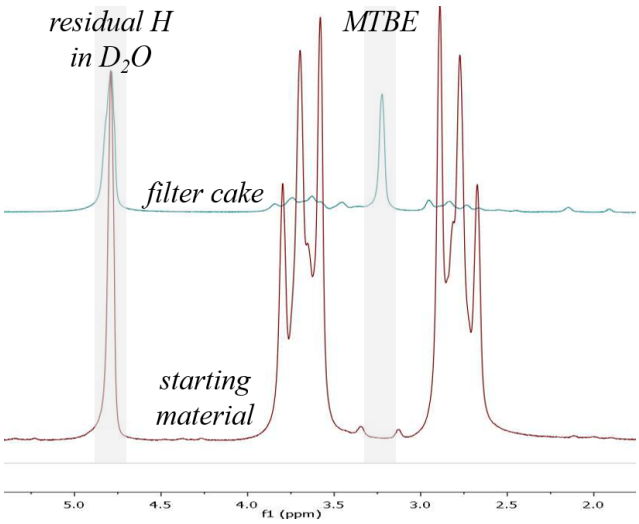


Fig. 4 Low-field NMR of the filter cake in reaction **4a**

mixture indeed contained the hydrochloride of the starting material (**4a.HCl**). Even though K_2CO_3 has a pK_a value of 10.3, **4a** (pK_a: 9.0) is competing for capturing the forming hydrochloric acid. Unfortunately, the previously mentioned solubility issues did not allow organic extraction for quantification.

Upon isolation of **6a** from MTBE, the hygroscopic properties of the obtained oil lead to absorption of water from air, preventing it from redissolving in MTBE. Nonetheless, it was confirmed by low-field benchtop NMR that the oil did not decompose

In order to enhance the stability of the aminoketone, the hydrochloride (**7a**) was formed by adding equimolar amount of HCl in dioxane to the solution of the intermediate (Table 1, Entry 2,4: Methods A and B). A faint-yellow solid readily precipitated from the organic solution; however, during filtration contact with air still resulted in quick absorption of water.

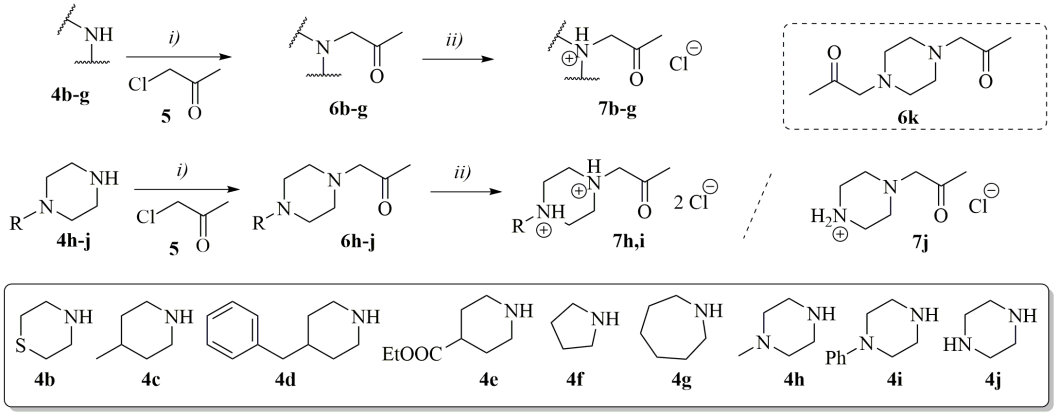
Under inert atmosphere, the product could be successfully isolated; furthermore, after drying, the obtained solid showed enhanced stability on air; even after 24 h standing on air the solid form was maintained.

This methodology was then applied for the synthesis of several further heterocyclic aminoketones (Table 2). As expected, the higher pK_a values resulted in shorter reaction times compared to **4a**. This trend can be observed when comparing the reactions using external base as well. In most cases, the reactions by Method A (with K_2CO_3) required more time to complete (except for **4d**). However, despite the shorter reaction time, considerably lower yield was observed when using an external base. Since in this case the filter cake also contained the starting material, the shorter reaction time is the consequence of the starting material's precipitation as a hydrochloride salt. In three cases (**4d**, **4e** and **4f**), the ketones were synthesized with high yields; however, the hydrochloric salts could not be isolated. Upon addition of the HCl in dioxane, the resulting hydrochloride salt stayed in a gummy state without precipitation. In addition, in case of **4f**, the starting material's hydrochloride did not precipitate either, but rather appeared as a dark-brown oil that could be separated by decanting the solution of the product. It is important to note, that in most cases the hydrochlorides possessed enhanced stability; however, two derivatives (**7b** and **7g**) liquefied quickly.

As piperazine (**4j**) is the most commonly applied saturated amine heterocycle for the synthesis of the active pharmaceutical ingredients mentioned in the *Introduction*, the reactions of this compound were more thoroughly explored. Analogous to the heterocycles bearing one secondary amine function, monosubstituted piperazine derivatives (**4h** and **4i**) can be only monoalkylated on the free amine group, while piperazine itself offers the possibility of symmetric dialkylation as well. Furthermore, when the piperazine derivatives possess two tertiary amine groups, two equivalents of HCl are required for precipitation, in contrast to monoalkylated compounds, where the product is precipitated with one equivalent. In case of 4h, the two reaction modes gave comparable yields, whereas the reactions of **4i** resulted in 30 % difference between yields (Table 2, Entry 8) indicating, that as in case of **4a**, this starting material might be precipitating in hydrochloride form as well. After confirmation *via* low-field NMR (Fig. 5), an aqueous-organic work-up of the filter cake successfully recovered non-water soluble **4i**.

Finally, the two examined reaction methodologies provide synthesis for both the mono- (**6j**) and dialkylated (**6k**) piperazine derivatives (Table 2, Entry 9). The preference for the different products can be understood when looking at the different reaction pathways (Fig. 6). When the inorganic external base is present (Method A), the monoalkylation reaction is complete in a few minutes forming **6j**, which then further reacts with **5**, forming the desired **6k**. Applying Method B reaction conditions for substrate **4j** results in **6j** as major product, since extra addition of **5** leads to the precipitation of **6j** hydrochloride, thus **6k** cannot be synthesized with high yield. Although in theory this methodology is suitable for the selective synthesis

Table 2 Alkylation of saturated heterocyclic amines (**4b-j**) with chloroacetone (**5**)



Entry	Amine	pK_a [a]	Aminoketone	Method	Reaction time (h)	6 yield[b] (%)	7 yield[b] (%)
1	**4b**	9.1	**6b**	**A**	4	88	73[b]
				B	4	100	83[b]
2	**4c**	10.7	**6c**	**A**	4	92	83
				B	2.5	100	85
3	**4d**	10.6	**6d**	**A**	2.5	59	-
				B	3.5	98	-
4	**4e**	9.8	**6e**	**A**	5	94	-
				B	4	93	-
5	**4f**	10.5	**6f**	**A**	6.5	81	-
				B	4	64	-
6	**4g**	10.3	**6g**	**A**	6	94	95
				B	4.5	100	66
7	**4h**	9.3	**6h**	**A**	12	82	76
				B	6	87	78
8	**4i**	9.0	**6i**	**A**	9	72	62
				B	12.5	99	91
9	**4j**	9.6	**6k**	**A**	7	64	42
			6j	**B**	8	n.d.[d]	74[e]

[a] Calculated by ACD/Labs Percepta, [b] Reaction conditions: *i*) **Method A**: saturated heterocyclic amine **4b-j** (1000 µL), **5** (1.1 equiv.) and K_2CO_3 (1.5 equiv) in 10 mL MTBE, reflux; **Method B**: saturated heterocyclic amine **4b-g** (1000 µL) and **5** (0.5 equiv.) in 10 mL MTBE, reflux. *ii*) HCl (1.05 equiv. for **4a-g,j**; 2.05 equiv. for **4h,i**) in dioxane, [c] The forming hydrochloride was recrystallized from ethanol/MTBE, [d] Not isolated, due to the complex reaction mixture, [e] NMR yield (For experimental procedures and analytical characterization see Supplement.)

of **6j**, the desired product could not be completely isolated from the unreacted starting material and side-product **6k**. The ^{1}H-NMR spectrum and the HRMS chromatogram of the crude mixture show that both **6k** and **4j** are present alongside with the desired product **6j**. After addition of equimolar amount of HCl, the NMR and HRMS analyses of the precipitate indicate a mixture of **7j** and **4j. HCl**, as **6k** requires two equivalents of HCl for precipitation. However, in the synthesis of the mono-alkylated compound, Method B does not make it possible to separate the monoalkylated **6j** from the starting material.

3 Conclusions

In this work, two simple and robust methods were compared for the synthesis of various saturated heterocyclic aminoketones. The improved workup procedures do not need chromatographic purification due to selective precipitation of the hydrochloride form from the reaction media. The hydrochloride forms of the target compounds were obtained in good to excellent yields and showed enhanced stability on air compared to the free base forms. Furthermore, new compounds have been also synthesized with the developed methods.

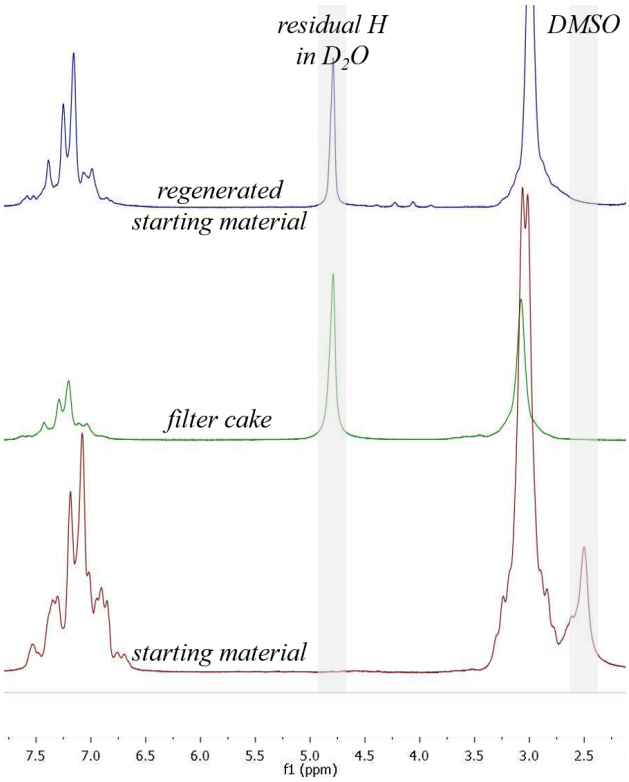


Fig. 5 Low-field NMR of the filter cake in reaction of **4i**

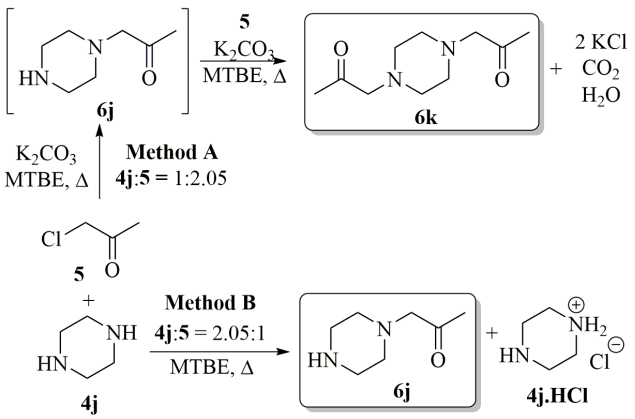


Fig. 6 Methods for alkylation of piperazine (**4j**) with chloroacetone (**5**)

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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