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The rearrangement of cyclopropylketone arylhydrazones. Synthesis of tryptamines and tetrahydropyridazines

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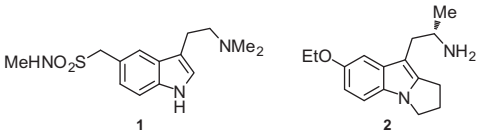
ABSTRACT

The cyclopropyliminium rearrangement of cyclopropylketone arylhydrazones may result in two possible products. The first one forms via cyclopropane ring-opening and ring-closure to give six-membered tetrahydropyridazines. The second is formed via ring-closure resulting in a five-membered ring and subsequent Grandberg rearrangement into a tryptamine. The product ratio depends on the nature of the starting hydrazones.

Tryptamine derivatives are psychoactive compounds and are widely used as 5-HT agonists. For example, compound **1** (Sumatriptan)[1] is used for the treatment of migraine, while compound **2**[2] has demonstrated high potential for the treatment of obesity.



Derivatives of 1,4,5,6-tetrahydropyridazine, in turn, have not been screened in detail for their biological activity. They are described as nonsteroidal progesterone receptor ligands[3] and antibacterial drugs.[4]

There are numerous methods available for the synthesis of tryptamines, many of which[5a–o] consist of modifications of other indole derivatives. Fleming et al.[6] suggested a pathway to *N*,*N*-dialkyltryptamines via the amination and aminomethylation of 2-bromophenyl vinyl ketone followed by the formation of an indole ring. Nicolaou et al.[7] synthesized tryptamine by the reaction of Boc-aniline with *N*-Boc-3-pyrrolidone in the presence of a strong base with subsequent decarboxylation and cyclization. Recently, a Pd-catalyzed reaction of 2-iodoanilines with protected γ-aminobutanal to form tryptamines was reported.[8] Nevertheless, in most cases, the syntheses of tryptamine derivatives are based on the Fischer indolization reaction. Since aminoaldehydes and ketones can be unstable, synthetic methods often demand the use of their precursors and latent forms.[9a–d] One of these methods reported by Grandberg[9d] involves the cyclization of γ-chloroketone arylhydrazones into *N*-(arylamino)pyrrolines, which in turn rearrange into tryptamines by analogy to the Fischer synthesis mechanism.

In contrast, methods for the synthesis of 1,4,5,6-tetrahydropyridazines, are scarce. Thus, in some cases, the cyclization of γ-chloroketone arylhydrazones, besides tryptamine derivatives, leads to the formation of tetrahydropyridazines.[10] Several syntheses of various alkaloids are based on this method.[11,12] Tetrahydropyridazine derivatives form in the reactions of 3-acylpropionic acids with hydrazines,[13] in the rearrangement of bicyclic diaziridines,[14] and in the reaction of vinyl carbenes with aromatic aldehyde hydrazones.[15]

It should be noted that the Grandberg method is general for the synthesis of both tryptamines and tetrahydropyridazines. In these transformations, hydrazones were generated directly from chloroketones and arylhydrazines. Subsequently, a few examples of their generation from haloalkynes were reported in the literature.[16,9c] Here we report that cyclopropylketone arylhydrazones, which can undergo cyclopropane ring-opening as in the cyclopropyliminium rearrangement,[17,18] are used to form haloketone hydrazones and subsequently tetrahydropyridazines and tryptamines. Thus we

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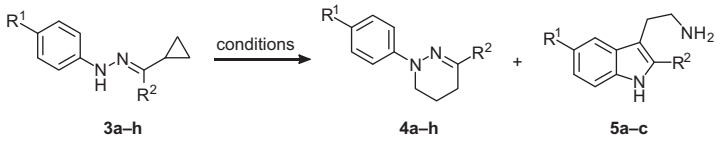
Table 1
Rearrangement of cyclopropyl ketone arylhydrazones



Entry	Hydrazone	R^1	R^2	Conditions	Products (yields, %)	
1[a]	**3a**	H	Me	NH_4I, MeCN, Δ	**4a** (34)	**5a** (49)
2[a]	**3b**	Br	Me	HCl, EtOH, Δ	**4b** (5)	**5b** (80)[b]
3	**3c**	NO_2	Me	NH_4I, DCB,[d] Δ	**4c** (31)	**5c** (25)[c]
4[a]	**3d**	H	Ph	NH_4I, MeCN, Δ	**4d** (69)	—
5[a]	**3e**	Br	Ph	HCl, EtOH, Δ	**4e** (54)	—
6	**3f**	NO_2	Ph	NH_4I, DCB,[d] Δ	**4f** (44)	—
7[a]	**3g**	H	*cyclo*-C_3H_5	NH_4I, MeCN, Δ	**4g** (60)	—
8	**3h**	NO_2	*cyclo*-C_3H_5	NH_4I, DCB,[d] Δ	**4h** (45)	—

[a] Hydrazones were generated in situ from ketones and either 4-bromophenylhydrazine hydrochloride or phenylhydrazine.
[b] The product was obtained as the hydrochloride.
[c] The product was obtained as the hydroiodide.
[d] 1,2-Dichlorobenzene.

can simplify the Grandberg method by using stable cyclopropylketones instead of highly reactive haloketones.

We are aware of two previous publications on cyclopropylketone hydrazone rearrangements. In one of these the authors[19] stated that tryptamines were the only reaction products, since they obtained only water-soluble hydrochlorides. In the second,[20] the reaction of cyclopropyl phenyl ketone with phenylhydrazine in hydrochloric acid in ethanol gave a mixture of 3-methyl-1-phenyl-1,3,5,6-tetrahydropyridazine (26%) and 2-phenyl-3-(2-chloroethyl)indole (17%). In this article we present an investigation of the rearrangement of cyclopropylketone arylhydrazones as a method for the synthesis of tryptamines and tetrahydropyridazines; nitro group containing hydrazones were synthesized in a separate reaction step, the others being generated in situ.

We have found that cyclopropyl methyl ketone hydrazones **3a–c** (Table 1, entries 1–3) rearrange into a mixture of tetrahydropyridazines **4a–c** and tryptamines **5a–c**, the best yield of the tryptamine being observed in the case of in situ generated bromophenylhydrazone **3b**[21] (entry 2). At the same time, cyclopropyl phenyl ketone hydrazones **3d–f**, and dicyclopropyl ketone phenyl- and 4-nitrophenylhydrazones **3g** and **3h** rearrange to give tetrahydropyridazines **4d–h** exclusively. In contrast to phenyl- and 4-bromophenylhydrazones, which rearrange under relatively mild conditions, 4-nitrophenylhydrazones require more stringent reaction conditions, that is, heating in 1,2-dichlorobenzene (DCB).

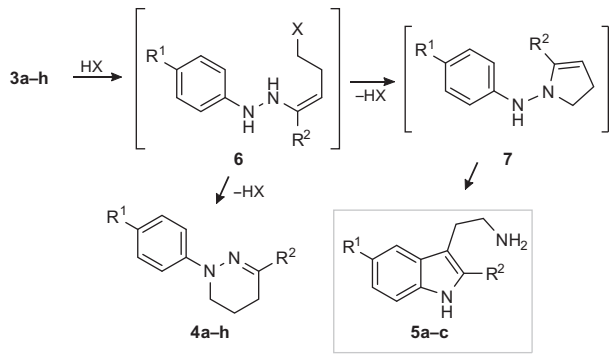
The first stages of these transformations correspond to those of the cyclopropyliminium rearrangement and include protonation and cyclopropane ring-opening to form halides **6**, which undergo ring-closure into tetrahydropyridazines **4a–h** (Scheme 1). The formation of tryptamines **5a–c** from halides **6** can proceed via two possible mechanisms, analogous to those described by Grandberg et al.[10] The first consists of the ring-closure to give a five-membered pyrroline **7**, followed by rearrangement into tryptamines **5a–c** analogous to the Fischer indole synthesis (Scheme 1). It is worth noting that despite the apparent spatial restriction of the sigmatropic rearrangement of **7** due to the presence of the pyrroline ring, there is an example of a Claisen rearrangement with structures similar to these.[22]

However, the rearrangement accompanied by N–N bond cleavage can proceed before elimination of hydrogen chloride, in other words, via the formation of imine **8**, which transforms into tryptamines via several straightforward steps (Scheme 2).

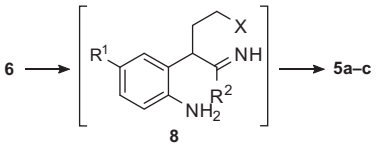
It is worth mentioning that tetrahydropyridazine **4d** was previously obtained by Grandberg et al.[10] by the reaction of phenylhydrazine and 3-chloropropyl phenyl ketone in a similar yield (52%) indicating that the two processes are similar in mechanism.

In the case of dicyclopropyl ketone 4-bromophenylhydrazone (**9**), which is generated in situ from the corresponding hydrazine **10** and ketone **11**, instead of the expected 2-cyclopropyltryptamine **12**, we obtained tryptamine **13**, which forms via ring-opening of both cyclopropyl rings, in a mixture with a smaller amount of tetrahydropyridazine **14**. It is thought that hydrazone **9** initially transforms into di(chloropropyl) ketone hydrazone **15**. Intramolecular alkylation of the latter leads to the formation of **16**, which in turn rearranges into **13** through the intermediate pyrroline **17** (Scheme 3).

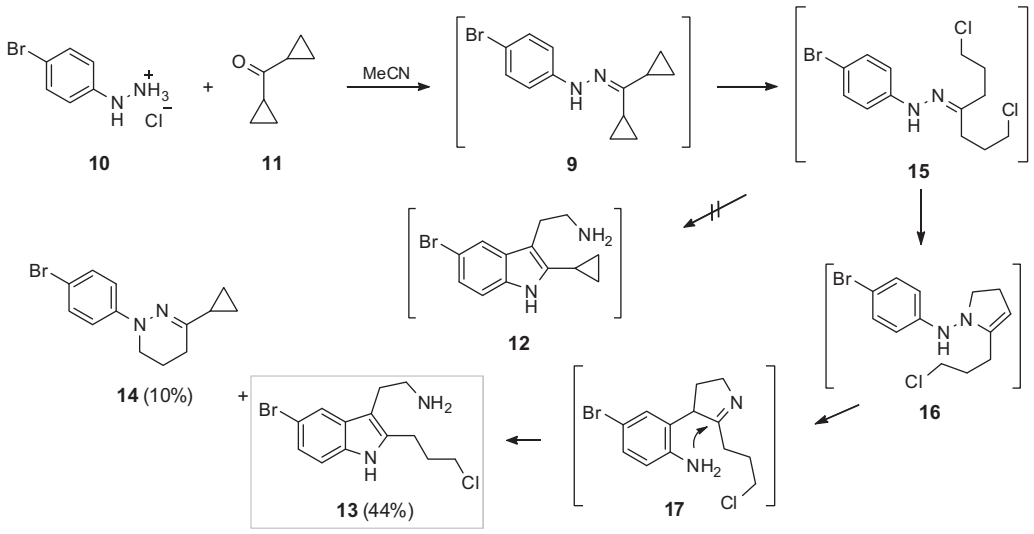
Specific reaction products were observed in the rearrangement of cyclopropyl methyl ketone 2,4-dinitrophenylhydrazone (**18**) under heating with NH_4I in DCB. Apparently, hydrazone **18** primarily transforms into a mixture of the corresponding pyrroline **19** and tetrahydropyridazine **20**, analogous to the aforementioned hydrazones. The latter further rearranges into benzotriazole oxide **21**,



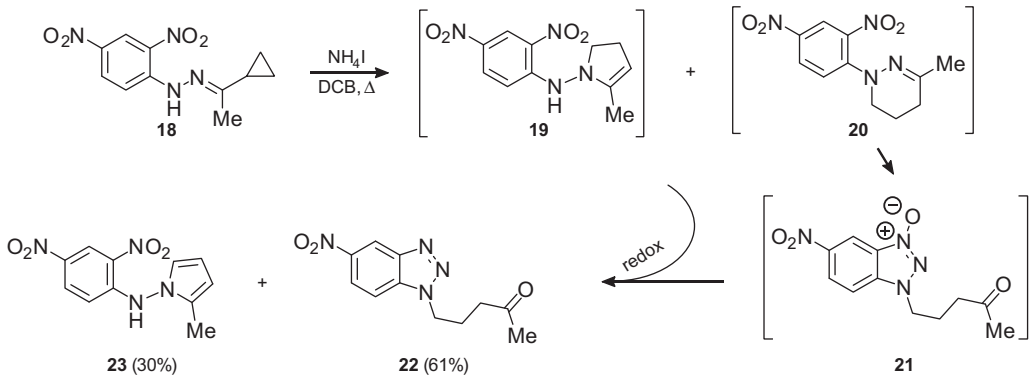
Scheme 1. Proposed mechanism for the formation of tetrahydropyridazines and tryptamines via the generation of a pyrroline ring.



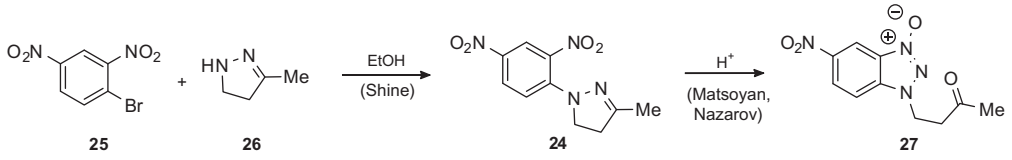
Scheme 2. Proposed mechanism for the formation of tryptamines via rearrangement of haloketone arylhydrazones.



Scheme 3. Rearrangement of dicyclopropyl ketone 4-bromophenylhydrazone.



Scheme 4. Rearrangement of cyclopropyl methyl ketone 2,4-dinitrophenylhydrazone.



Scheme 5. Rearrangement of 1-(2,4-dinitrophenyl)-3-methylpyrazoline (**24**) into 5-nitro-1-(3-oxobutyl)benzotriazole 3-oxide (**27**).

which in turn undergoes a redox reaction with pyrroline **19** to give a mixture of benzotriazole **22** and pyrrole **23**. Since the product ratio is not equimolar, oxide **21** presumably eliminates atomic oxygen, which is partially consumed in the oxidation of **19** (Scheme 4). Dicyclopropyl ketone and cyclopropyl phenyl ketone dinitrophenylhydrazones, under these conditions, slowly decompose to form dinitrophenylhydrazine.

Previously Shine et al.[23] synthesized pyrazoline **24** via the reaction of **25** and **26** (Scheme 5) and found that its characteristics did not coincide with those reported earlier by Matsoyan and Vartanyan,[24] which in turn agreed with those of the product of unknown structure obtained by Nazarov et al.[25] The authors investigated the previous results and demonstrated that in acidic medium, pyrazoline **25** (homologous to **20**) undergoes rearrangement into benzotriazole oxide **27** (homologous to the intermediate **21**), which was in fact the product obtained by Matsoyan and Nazarov. Thus, the rearrangement analogous to that of **20** into **21** was described previously, in our case oxide **21** is not observed due to the stringent reaction conditions.

In conclusion, the rearrangement of cyclopropyl methyl ketone phenyl-, 4-bromophenyl-, and 4-nitrophenylhydrazones proceeds to form a mixture of tetrahydropyridazines and tryptamines, the formation of the latter being due to the Cloke–Stevens–Grandberg domino rearrangement. Cyclopropyl phenyl ketone phenyl-, 4-bromophenyl- and 4-nitrophenylhydrazones and dicyclopropyl ketone phenyl- and 4-nitrophenylhydrazones only rearrange into tetrahydropyridazines, while in the case of dicyclopropyl ketone 4-bromophenylhydrazone the tryptamine derivative is formed via ring-opening of both cyclopropyl rings. Cyclopropyl methyl ketone 2,4-dinitrophenylhydrazone rearranges into a mixture of benzotriazole and pyrrole derivatives. We have shown that the rearrangement of electron-deficient hydrazones requires stringent reaction conditions. As a result, we have studied in detail the rearrangement of cyclopropyl ketone hydrazones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.017.

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21. Reaction of cyclopropylethanone with 4-bromophenylhydrazine and subsequent rearrangement. A mixture of 4-bromophenylhydrazine hydrochloride (1.48 g, 6.6 mmol), and cyclopropyl methyl ketone (1.00 g, 12 mmol) in EtOH (20 mL) was heated at reflux for 7 h. The hot mixture was diluted with H_2O (14 mL) and cooled to rt. The resulting precipitate was filtered and purified by column chromatography (cyclohexane–EtOAc, 2:1) to give **4b** (0.084 g, 5%). The filtrate was evaporated and recrystallized from MeOH–$CHCl_3$ (1:4) to give **5b** (1.38 g, 80%).
*Compound **4b**:*, brownish crystals, mp 85–86 °C; IR (KBr) 3090, 3040, 2970, 2927, 2864, 1588, 1491 cm^{-1}. EIMS (*m*/*z*, %) 252, 254 (both 100, M^+), 237, 239 (9, M^+-CH_3), 183, 185 (20), 182, 184 (30), 155, 157 (38, BrC_6H_4). ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 2H), 7.10–7.02 (m, 2H), 3.47–3.38 (m, 2H), 2.12–2.18 (m, 2H), 2.07–1.94 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 144.5, 131.7, 115.1, 111.3, 42.2, 25.6, 24.4, 19.0. Anal. Calcd for $C_{11}H_{13}BrN_2$: C, 52.19; H, 5.18; N, 11.07. Found: C, 50.79; H, 5.18; N, 11.04.
*Compound **5b**·**HCl**:*, brownish crystals, mp 254–255 °C; IR (KBr) 3355, 3312, 2963, 2935, 2909, 2888, 2844, 2741, 2020, 1493, 1468, 1453, 1433 cm^{-1}. EIMS (*m*/*z*,%) 252, 254 (both 7, M^+-HCl), 223, 225 (26), 183, 185 (46), 143 (20), 30 (100, $CH_2NH_2^+$). ^1H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H, NH), 8.12 (s, 3H, NH_3), 7.66 (d, *J* = 1.9 Hz, 1H, H(4)), 7.22 (d, *J* = 8.5 Hz, 1H, H(7)), 7.09 (dd, *J* = 8.5, 1.9 Hz, 1H, H(6)), 3.04–2.77 (m, 4H, CH_2CH_2), 2.34 (s, 3H, Me). ^{13}C NMR (75 MHz, DMSO-d_6) δ 134.8, 133.9, 129.8, 122.5 (C(6)), 119.4 (C(4)), 112.5 (C(7)), 111.0, 105.4, 39.4 (CH_2), 21.7 (CH_2), 11.2 (CH_3). Anal. Calcd for $C_{11}H_{14}BrClN_2$: C, 45.62; H, 4.87; N, 9.67. Found: C, 45.43; H, 4.89; N, 9.64.
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