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APPLICATION OF HEXAMETHYLENETETRAMINE IN A PICTET- SPENGLER TYPE REACTION FOR SYNTHESIS OF ISOQUINOLINE DERIVATIVES

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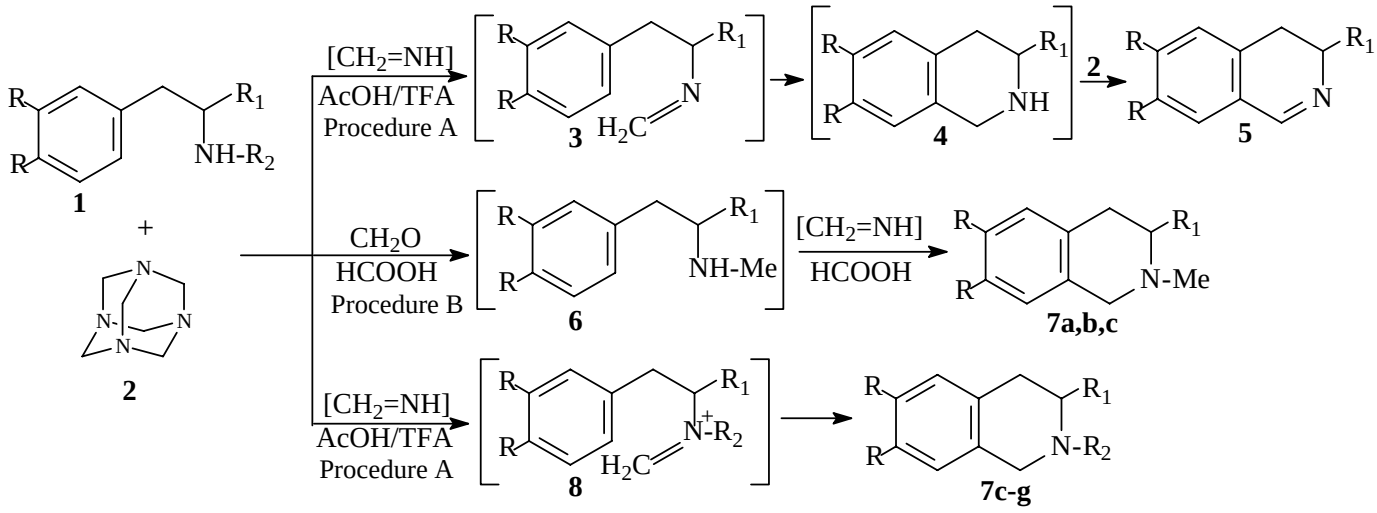
Abstract- Hexamethylenetetramine was used successfully as amino- and amidoalkylation cyclization reagent for the synthesis of 3,4-dihydroisoquinolines, tetrahydroisoquinolines and 1,4-dihydro-3(2*H*)-isoquinolinones. The reagent provides a simple and convenient pathway for the preparation of a range of these compounds.

Hexamethylenetetramine (HMTA) as a reagent has been used as a source of -CH=N- and -CH= functions. It has been employed for introduction of formyl group usually in activated aromatic compounds (Sommelet and Duff reactions), for the synthesis of *N*-heterocyclic compounds[1,2] and as a Mannich reagent in the reactions with alkyl aryl ketones.[3] Here, we report the results of our efforts to use hexamethylenetetramine as a ready available reagent for synthesis of isoquinoline derivatives since many of them are known as alkaloids and pharmaceutically active compounds.[4]

It was found that the reaction of 2-phenylethylamines (**1**) with HMTA (**2**) led surprisingly but readily only to 6,7-dimethoxy-3,4-dihydroisoquinolines (**5**) (Scheme 1, Table 1, **5a, b**)**.** The reaction was carried out in a mixture of glacial acetic and trifluoroacetic acids (ratio 4:1) at a reflux for 15 min or in PPA for 30 min at 80^{o}C. The reactions were successful only in the presence of activating groups in the aromatic ring of 2-phenylethylamines (**1**) (R=MeO) as are the requirements for Bischler-Napieralski cyclization to 3,4-dihydroisoquinolines from their amides. Two feasible routs are possible to **5**: formylation of the activated aromatic ring of **1** (Duff reaction) and then spontaneous cyclization to **5** or Pictet-Spengler's cyclization to **4** of an iminium intermediate (**3**) and then its oxidation to **5** from HMTA. Several experiments were carried out for clarification of the reaction route. We found that 6,7-dimethoxytetrahydroisoquinoline (**4a**) (as base or hydrochloric salt), 1-phenyl- or 1-methyl-6,7-dimethoxytetrahydroisoquinoline as well as tetrahydroisoquinoline can be converted to their 3,4-dihydro derivatives in good yields with HMTA in a mixture of glacial acetic and trifluoroacetic acids (ratio 4/1) at a reflux of the reaction mixtures for 10 min. Similar oxidation with HMTA of 1,4-benzodiazepines to the corresponding imines is known from the literature.[5] It was found also that the reaction of *N*-methyl-3,4-dimethoxy-2-phenylethylamine (**6**) (Scheme 1, R=OMe, R_1=H) with HMTA at the same reaction conditions afforded *N*-methyl-6,7-dimethoxytetrahydroisoquinoline (Procedure A, Table 1, **7c**, 94%

yield) as a result of an intramolecular aminoalkylation. Our efforts for formylation of 1,2-dimethoxybenzene with HMTA at the same reaction conditions (Duff reaction) were unsuccessful. The above results and the fact that the reaction of **1** without activating groups in the aromatic ring (R=H) with HMTA to **5** was not successful leads to the assumption that the reaction proceeds through **3** and **4** as intermediates. The procedure can be regarded as a variation of Bischler-Napieralski method for synthesis of 3,4-dihydroisoquinolines and an advantage of this approach is the successful synthesis of 3-substituted 3,4-dihydroisoquinolines as **5b.** Similar yields of 3,4-dihydroisoquinolines were obtained when the above reactions were carried with *N*-ethylmethanimine (1,3,5-triethylhexahydrotriazine) instead of HMTA.



Scheme 1

Table 1. Isoquinoline derivatives (**5**) and (**7 a-g**) produced *via* Scheme 1

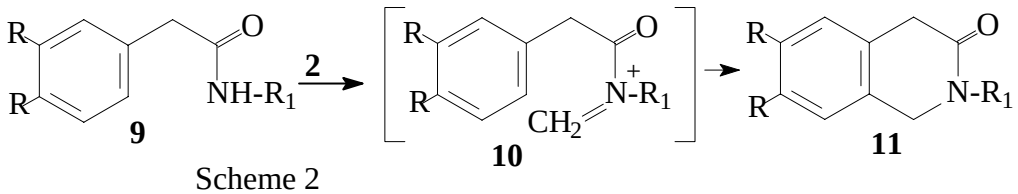
Entry	R	R_1	R_2	Yields (%)		Ref.
				5	**7**	
1a	MeO	H	H	90[a]	78[b]	4
1b	MeO	3,4-$(MeO)_2C_6H_3$	H	86[a]	58[b]	6
1c	MeO	H	Me	-	94[a](93)[b]	4
1d	MeO	H	COOEt	-	92[a]	7
1e	H	H	COOEt	-	77[a]	8
1f	MeO	H	CONHPh	-	90[a]	9
1g	H	H	CONHPh	-	85[a]	10

[a]Procedure A; [b]Procedure B.

The reaction of HMTA with 2-phenylethylamines using formic acid as a solvent at reflux of the reaction mixture for 1 h afforded *N*-methyltetrahydroisoquinolines (**7a,b**) (Scheme 1, Procedure B) and traces of the corresponding **5** (Table 1). Thus, the reaction of **1a** (R=MeO, R_1=R_2=H) with HMTA in HCOOH at a reflux afforded 78% of **7a** and 10% of **5a** while the reaction of *N*-methyl-3,4-dimethoxy-2-phenylethylamine (**1c**) with HMTA led only to *N*-methyl-6,7-dimethoxytetrahydroisoquinoline (**7c**) (Procedure B, Table 1, yield 93%). Our attempts to carry out a reductive methylation of 6,7-dimethoxy-3,4-dihydroisoqunoline to **7a** with HMTA at the same reaction conditions (1 h reflux in HCOOH) were

unsuccessful. It can be assumed that the reaction mode is probably as this of Eschweiler-Clark method and included methylation of nitrogen in **1** to **6** and then cyclization to **7**.

Next, we investigated of the reaction of HMTA with secondary amides of 2-phenylethylamines. We found that the reaction of *N*-acyl-2-phenylethylamines (**1d,e**), *N*-phenyl-2-phenylethylureas (**1f,g**) and phenylacetamides (**9**) with HMTA in AcOH/TFA (4/1) afforded the corresponding *N*-acyl-tetrahydroisoquinolines (Table 1, **7d,e**), *N*-carbamoyltetrahydroisoquinolines (Table 1, **7f,g**) and 1,4-dihydro-3(2*H*)-isoquinolinones (Scheme 2, Table 2, **11a,b**). The cyclization reaction of HMTA with amides (**1**) was successful also in the cases when there are not activating groups in the aromatic ring (Table 1, **7e,g**).



Scheme 2

Table 2. 1,4-Dihydro-3(2*H*)-isoquinolinones

11	R	R_1	Yield (%)	Ref.
a	MeO	H	72[a]	11
b	MeO	Me	77[a]	12
c	H	Me	62[c]	13
d	H	Et	58[c]	14

[a]Procedure A; [c]Procedure C.

The reaction of HMTA with phenylacetamides (**9**) is also successful when there are no activating groups in the aromatic ring but only in PPA at 80°C for 3 h (Procedure C, Table 2, **11c,d**). It can be assumed from the obtained results that the reaction is an intramolecular amidoalkylation with the formation of *N*-acyliminium ions (**10**). The successful cyclization and formation of isoquinoline derivatives (**11e,g)** (Table 1) and (**11c,d**) (Table 2), without activating groups in the aromatic ring, can be assign to the stronger electrophilicity of the corresponding *N*-acyliminium ions (**10**)**.**

The results above demonstrate the application of HMTA as inexpensive and easily available reagent for synthesis of variety of isoquinoline derivatives as a result of an intramolecular amino- and amidoalkylation reactions. The convenient one-pot preparation of 3,4-dihydroisoquinolines from 2-phenylethylamines and HMTA is a Pictet-Spengler reaction combined with an oxidation process.

EXPERIMENTAL

All of the obtained isoquinoline derivatives (**5, 7, 11**) were characterized by their mp, IR and NMR spectra and compared with the data known from the literature.

Preparation of 3,4-Dihydroisoquinolines (5), *N*-Acyltetrahydroisoquinolines (7) and 1,4-Dihydro-3(2*H*)-isoquinolinones (11) (Procedure A): To a solution of 2-phenylethylamine or the corresponding amide (3 mmol) in a mixture of AcOH/CF_3COOH (4 mL:1 mL) is added HMTA (841 mg, 6 mmol) and the reaction mixture is refluxed for 30 min (for **5a,b** and **7d,g**), 3 h at reflux (for **7e**), overnight at rt (for **7f**) or 1 h at reflux (for **11a,b**). The cooled solution is diluted with water (50 mL), basified with Na_2CO_3, and extracted with CH_2Cl_2 (3x20 mL). The combined extracts were dried (Na_2SO_4), the solvent removed and the products were purified by filtration through a column with basic or neutral Al_2O_3 using CH_2Cl_2 as eluent.

Preparation of *N*-Methyltetrahydroisoquinolines (7a-c) (Procedure B**):** The reaction is carried with 3 mmol of amine, 6 mmol (841 mg) of HMTA in 100% HCOOH (10 mL) at reflux for 1 h and the reaction mixture is worked up as above.

Preparation of 3,4-Dihydroisoquinolines (5a) and 1,4-Dihydro-3(2*H*)-isoquinolinones (11c,d) (Procedure C): 2-Phenylethylamines (**1**) or phenylacetamides (**9**) (3 mmol) and HMTA (841 mg, 6 mmol) in PPA (10 g) is heated for 30 min at 80^{o}C (for **5a**) or 3 h (for **11c,d**). The reaction mixture is poured on a crash ice and then worked as above.

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