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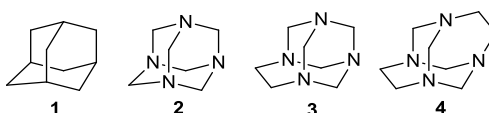
SYNTHESIS AND CHARACTERIZATION OF PHENYL(1,3,6,8-TETRAAZATRICYCLO[4.3.1.1^{3,8}] UNDECAN-4-YL)- METHANONE AND ITS DERIVATIVES

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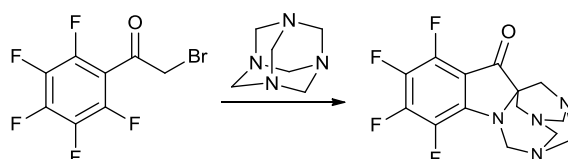
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Abstract – A quick and highly efficient method for the synthesis of phenyl(1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecan-4-yl)methanone and its derivatives from hexamine and 2-bromo-1-arylethanones has been established via a Stevens rearrangement. Structures of the products were characterized by NMR and X-ray crystallography.

1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}]decane (hexamine or urotropine, **2**) is a cage aminal with structure like adamantane (**1**). It has been widely used in medicinal and materials chemistry, such as the production of phenolic resins and solid fuel tablets.^{1,2} Besides, hexamine is easily trapped by metal-organic compounds to form various molecular adducts.^{3,4} The ring-enlargement derivative of hexamine, 1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane⁵⁻⁷ (TATU, **3**), which is also applied in organic synthesis, has been the subject of structural and chemical research in recent years.^{8,9}

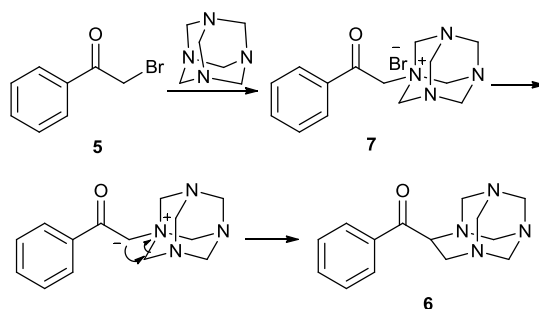


In 1999, Henry¹⁰ combined hexamine and pentafluorophenacyl bromide to generate a complex ring-enlargement product (Scheme 1). The reaction was performed in chloroform for over 24 h and the yield was low. In 2004, Rivera^{11,12} treated 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD, **4**) with ammonium fluoride in water to obtain TATU by cleavage of only one ethylene bridge. A variety of quaternary ammonium salts of TATU could be prepared by Menshutkin reaction.⁸ However, there have been few reports about modification of TATU at methylene. In this paper, a highly efficient method of synthesizing benzoyl-TATU was created.



Scheme 1. Reaction of pentafluorophenacyl bromide with hexamine

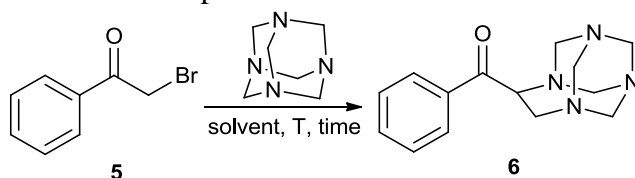
When heated at high temperature, hexamine slowly decompose into formaldehyde and ammonia. Based on this characteristics, we designed a new route to synthesize 4-phenyl-1*H*-imidazole from 2-bromo-1-phenylethanone (**5**) by employing hexamine to initiate the Debus condensation.¹³ However, hexamine was transformed into a ring-enlargement product, phenyl(1,3,6,8-tetraazatricyclo-[4.3.1.13,8]undecan-4-yl)methanone (**6**) in high yield before its decomposition. According to the literature, the mixture of hexamine and 2-bromo-1-phenylethanone yields bromine substitute ammonium salt (**7**) at room temperature.^{14,15} The result of our experiment indicated that **7** could transform to amine **6** when the temperature was more than 50 °C (Scheme 2). This transformation in higher temperature was never reported before. In Henry's literature,¹⁰ a ring-enlargement product of hexamine was obtained through an ortho fluorine elimination and two Stevens rearrangements (Scheme 1). If there was no fluorine on the benzene ring, a one step Stevens rearrangement would lead to benzoyl-TATU **6**. The Stevens rearrangement is a transformation from quaternary ammonium salts to amines in the presence of a strong base.¹⁶⁻²⁰ In this reaction, as hexamine itself is a strong base, no additional base was needed.



Scheme 2. Plausible mechanism for the Stevens rearrangement

Based on the initial result, several reaction parameters, such as solvent, temperature, and reaction time were successively investigated for the optimal reaction conditions. The results are shown in Table 1. The solvent optimization disclosed that DMF was the best reaction medium and gave 87% yield (Table 1, entry 5). Other solvents were found to go against this transformation, and much lower yields were observed (Table 1, entries 1-4, 6). Moreover, temperature was crucial for this process. High yields were obtained when the reactions were carried out at more than 50 °C (Table 1, entries 8, 9). Too long time or too high temperature could easily result in by-products (Table 1, entries 7, 13). The best result was achieved when the mixture was stirred at 70 °C for 1 h (Table 1, entry 12).

Table 1. Optimization of reaction conditions^a



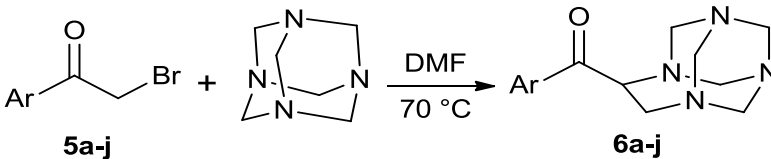
entry	solvent	T (°C)	time (h)	yield (%) ^b
1	anisole	90	2	19
2	toluene	90	2	29
3	ethylene glycol	90	2	67
4	pyridine	90	2	34
5	DMF	90	2	87
6	DMSO	90	2	23
7	DMF	110	2	81
8	DMF	70	2	89
9	DMF	50	2	82
10	DMF	30	2	32
11	DMF	70	0.5	84
12	DMF	70	1	90
13	DMF	70	3	88

^a hexamine (3 eq) was used.

^b isolated yield.

Having established the optimal reaction conditions, we explored the scope of this rearrangement process. A series of 2-bromo-1-arylethanones were examined. The results were shown in Table 2. Aromatic 2-bromo-1-phenylethanones **5a-h** with electron-neutral, electron-withdrawing or electron-donating substitutions at the benzene ring proceeded well to give good yields (Table 2, entries 1-8). Different substitution at benzene ring had little effect on the yield. This procedure was also performed well with heterocycle and fused ring substrates (Table 2, entries 9, 10). Furthermore, the structure of **6d** was confirmed by X-ray crystallography²¹ (Figure 2).

Table 2. Reaction scope of 2-bromo-1-arylethanones^a



entry	Ar	product	yield (%) ^b
1	Ph (5a)	6a	90
2	4-MeC ₆ H ₄ (5b)	6b	91
3	3-MeOC ₆ H ₄ (5c)	6c	89
4	4-MeOC ₆ H ₄ (5d)	6d	90
5	4-PhC ₆ H ₄ (5e)	6e	90
6	3-FC ₆ H ₄ (5f)	6f	92
7	4-ClC ₆ H ₄ (5g)	6g	93
8	4-CF ₃ C ₆ H ₄ (5h)	6h	93
9	2-thienyl (5i)	6i	92
10	2-naphthyl (5j)	6j	81

^a hexamine (3 eq) was used.

^b isolated yield.

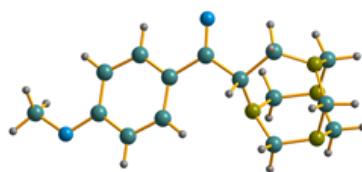


Figure 1. The X-ray molecular structure of **6d**

In conclusion, we have developed a highly efficient approach for the synthesis of phenyl(1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}undecan-4-yl)methanone and its derivatives from hexamine and 2-bromo-1-arylethanones through a Stevens rearrangement. The aminal can be converted to TATU in a short time with good yield. Further studies on the applications of the products will be reported in due course.

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21. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as Supplementary Publication, CCDC 953711.