Chlorotrimethylsilane-Promoted Condensation of Ketones and Aminoazoles

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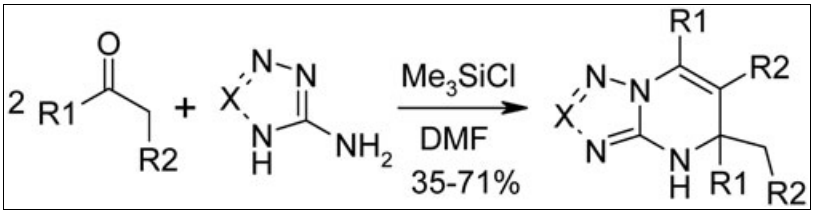

Chlorotrimethylsilane-promoted reaction of ketones and aminoazoles (*i.e.*, 3-amino-1,2,4-triazoles, 5-aminotetrazole) at 2 : 1 ratio resulted in the formation of 4,5-dihydroazolo[1,5-*a*]pyrimidine derivatives as the single regioisomers in 35 – 71% yields. In the case of *tert*-butylmethylketone and 5-aminotetrazole as the starting materials, the solvent (dimethylformamide) entered the reaction instead of the second ketone molecule.

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INTRODUCTION

Dihydropyrimidines represent a remarkable class of potential biologically active compounds. This can be explained by properties of the substituted dihydropyrimidine fragment which are commonly associated with "drug-likeliness" of the compounds, *i.e.,* hydrophilicity, nonflattened structure and chirality [1]. Dihydropyrimidine derivatives exhibit a range of biological activities; their representatives include calcium channel modulators, mitotic kinesine inhibitors, adrenergic receptor antagonists, antibacterial and antiviral agents [2]. Modern methods for synthesis of dihydropyrimidines allow preparation of the compounds with almost any substitution pattern [3–20]. On the contrary, fused dihydropyrimidine derivatives are much less explored.

It was demonstrated previously by our group and others that chlorotrimethylsilane is an efficient promoter of various condensations involving carbonyl compounds, *e.g.,* Knoevenagel, Friedlander, Biginelli and many other reactions [21–28]. As a part of our ongoing research on TMSCl-promoted reactions, we have turned our attention to the reaction of ketones **1** and aminoazoles **2** at 2:1 ratio resulting in the formation of azolopyrimidine derivatives **3** and/or **4** (Scheme 1). Although this transformation has been reported previously, mixtures of **3** and **4** were obtained in most cases; moreover, rather harsh conditions were used (150 – 190 °C; DMF [29], AcOH (or HCl) – DMF [30], $ZnCl_2$ – no solvent [31,32]). Apart from the single examples described in [29] and [31], no regioselective synthesis of the compounds of general formula **3** was reported to date.

In this work, we wish to report our results on chlorotrimethylsilane-promoted reaction of ketones **1a–c** and aminoazoles **2a–c** at 2 : 1 ratio. It was found that triazoles **2a,b** and tetrazole **2c** reacted with 2 eq of acetophenone (**1a**) in the presence of TMSCl (5 eq) – DMF at 100°C for 8 h to form the corresponding dihydroazolopyrimidine derivatives **3aa** – **3ac** in good yields (Table 1). Analogous reactions of cyclohexanone (**1b**) afforded the corresponding spiroheterocycles **3ba** – **3bc**, although with diminished outcome of the product. In all the cases, the condensation proceeded in a regioselective manner: no products **4** were detected in the crude reaction mixture.

The structure of the products **3** was confirmed by NOESY experiments performed with the compound **3aa**. First, 5- and 7-phenyl substituents were distinguished using correlation of *ortho*-protons with 5-methyl group, which is possible only for 5-phenyl. The correlation between 4-NH proton and *ortho*-protons of 7-phenyl group clearly confirm the structure **3aa** as it is impossible in the case of isomer **4aa** (Fig. 1).

Reaction of tetrazole **2c** with 2 eq of ketone **1c** under the conditions described led to the formation of tetrazolo[1,5-*a*]pyrimidine **5** in 78% yield (Scheme 2). In this case, due to the steric effect of *tert*-butyl substituent, dimethylformamide enters the reaction instead of the second molecule of *tert*-butylmethylketone. The structure of **5** was confirmed by comparison of chemical shifts in

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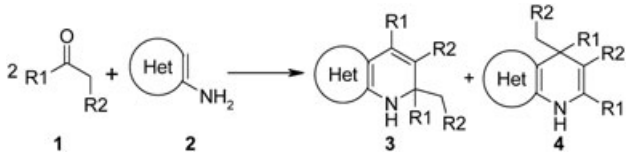
Scheme 1



^{13}C NMR with the literature data for the corresponding analogues **6** – **8** (Table 2) [33]. The chemical shift of the C-5 signal for the compound **5** is higher than that in the case of **8**; this is observed for 4-*tert*-butyl-substituted pyrimidines (see, for example, [34] and [35]). Moreover, vicinal coupling constant between protons at 6-C and 7-C in ^{1}H NMR spectra (7.3 Hz) is also consistent with the literature data for the analogues (6.9 – 7.3 Hz, while for the alternative isomers—4.2 – 4.8 Hz [36]).

The structure of **5** and the literature data [29,37,38] allows us to assume that the reaction of aminoazoles with ketones starts with electrophilic attack of the carbonyl group of the activated ketone molecule **9** at the amino group of the silylated aminoazole derivative **10** [21] (Scheme 3). Silylation of the starting aminoazole at the endocyclic nitrogen atom prevents attack of the ketone at this site, hence the reaction proceeds in a regiospecific manner. The second ketone molecule (or dimethylformamide, as in the case of the formation of **5**) reacts then with the imine intermediate **11** formed to accomplish the heterocyclization. It is interesting to note that the products analogous to **5** were also detected by LC–MS in the crude reaction mixtures obtained from ketones **1a** and **1b** and aminoazoles **2a–c** as the starting compounds. Unfortunately, replacing the DMF with other solvents to avoid these side reactions was unfruitful.

In conclusion, chlorotrimethylsilane-promoted reaction of ketones and aminoazoles at 2:1 ratio is an efficient method for the synthesis of azolo[1,5-*a*]pyrimidine derivatives. Using of chlorotrimethylsilane allows to obtain the corresponding products in a regiospecific manner and to perform the reaction under relatively mild conditions comparing to the procedures reported previously. The corresponding products are obtained as single isomers in 35–71% yields.

Table 1

Chlorotrimethylsilane-promoted reaction of ketones **1a–c** and aminoazoles **2a–c**.

Entry No.	Reagents		Product	R1	R2	X	Yield, %
1	**1a**	**2a**	**3aa**	Ph	Me	CH	65
2	**1a**	**2b**	**3ab**	Ph	Me	CCF_3	62
3	**1a**	**2c**	**3ac**	Ph	Me	N	71
4	**1b**	**2a**	**3ba**	$(CH_2)_4$		CH	40
5	**1b**	**2b**	**3bb**	$(CH_2)_4$		CCF_3	35
6	**1b**	**2c**	**3bc**	$(CH_2)_4$		N	46

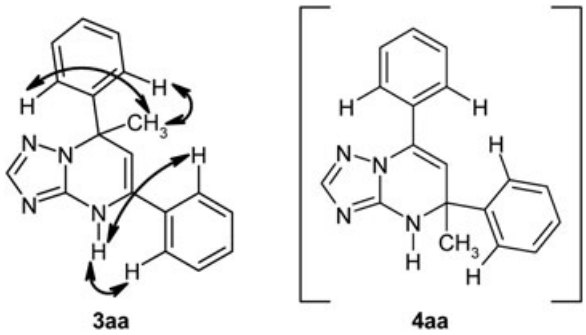


Figure 1. Significant NOESY correlations for the compound **3aa**.

EXPERIMENTAL

Solvents were purified according to the standard procedures. Compound **2b** was prepared by the procedure described in the literature [39]. All other starting materials were purchased from Acros, Merck, and Fluka. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C NMR, and all 2D NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for protons, 124.9 MHz for carbon-13) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for protons, 100.7 MHz for carbon-13). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. HPLC-MS analyses were done on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Kyiv National Taras Shevchenko University.

General procedure for the reaction of ketones 1a–c and aminoazoles 2a–c. A mixture of ketone **1** (0.4 mmol) and aminoazole **2** (0.2 mmol) was dissolved in dry DMF (1 mL) in an ace pressure tube, and then chlorotrimethylsilane (1 mmol) was added dropwise. The tube was sealed and heated on a steam bath for 8 h, then cooled and diluted with water (6 mL). The resulting mixture was sonicated for 2 h at 40°C, the precipitate was filtered and washed with a small amount of

Scheme 2

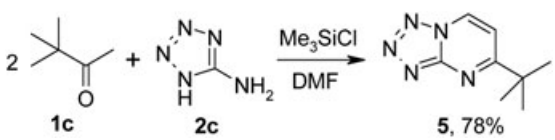
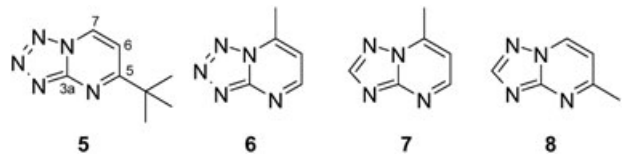


Table 2

Significant chemical shifts in ^{13}C NMR spectra of the compounds **5** – **8**.



5 **6** **7** **8**

Entry no.	Compound	^{13}C NMR, δ
1	**5**	153.6 (3a-C), 179.8 (5-C), 111.7 (6-C), 134.7 (7-C)
2	**6**	158.9 (3a-C), 158.4 (5-C), 112.4 (6-C), 146.8 (7-C)
3	**7**	156.0 (3a-C), 154.4 (5-C), 110.1 (6-C), 148.1 (7-C)
4	**8**	158.9 (3a-C), 165.7 (5-C), 111.2 (6-C), 135.0 (7-C)

*i*PrOH. The crude product was purified by flash chromatography (Hexane – EtOAc (9:1) as an eluent).

5-Methyl-5,7-diphenyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine 3aa. Yield 65%. Mp 174 °C. ^1H NMR (500 MHz, DMSO-d_6), δ: 2.09 (s, 3H), 5.29 (s, 1H), 7.26 (m, 3H), 7.34 (m, 3H), 7.41 (m, 2H), 7.61 (m, 2H), 7.69 (s, 1H), 9.97 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 28.7, 62.5, 103.4, 125.6, 126.3, 127.6, 128.8, 129.0, 129.4, 134.1, 134.5, 146.5, 150.0, 150.1. APCI MS: 289 (MH^+). Anal. calcd. for $C_{18}H_{16}N_4$ C 74.98, H 5.59, N 19.43. Found C 75.14, H 5.31, N 19.24.

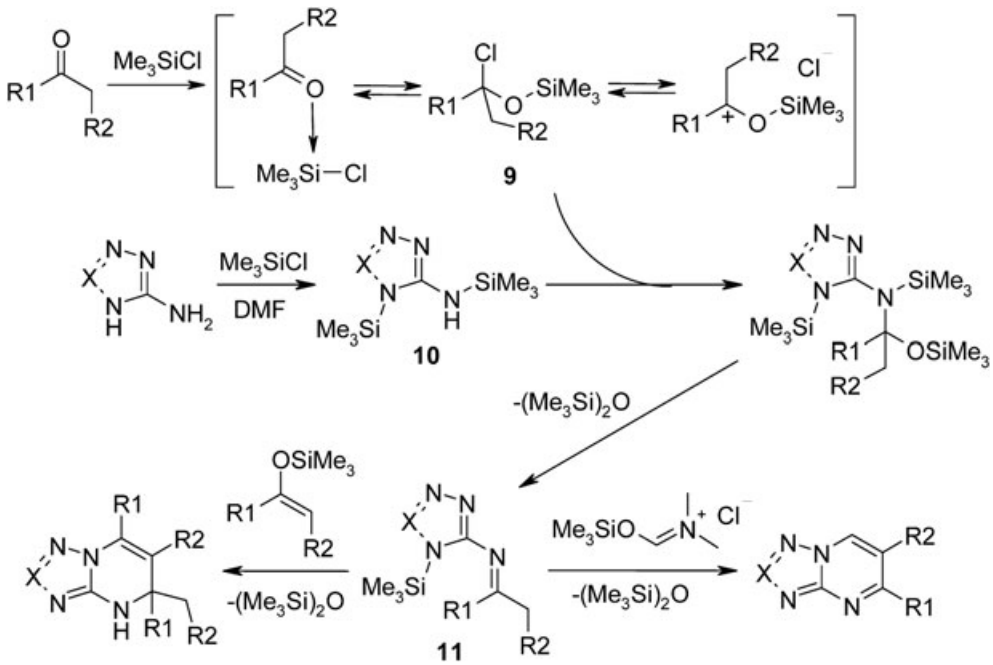
5-Methyl-5,7-diphenyl-2-(trifluoromethyl)-4,5-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine 3ab. Yield 62%. Mp 183 °C. ^1H NMR (500 MHz, DMSO-d_6), δ: 1.80 (s, 3H), 5.87 (s, 1H), 7.29 (m, 1H), 7.40–7.46 (m, 5H), 7.56–7.60 (m, 4H), 8.93 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 31.1, 58.1, 115.6, 119.9 (q, J = 270.3 Hz), 125.3, 127.7, 128.7, 128.9, 129.1, 129.9, 131.4, 132.9, 147.7, 150.3 (q, J = 38.4 Hz), 154.8. APCI MS: 357 (MH^+). Anal. calcd. for $C_{19}H_{15}F_3N_4$ C 64.04, H 4.24, N 15.72. Found C 64.29, H 4.03, N 15.97.

5-Methyl-5,7-diphenyl-4,5-dihydrotetrazolo[1,5-*a*]pyrimidine 3ac. Yield 71%. Mp 214 °C. ^1H (500 MHz, DMSO-d_6), δ: 2.21 (s, 3H), 5.41 (s, 1H), 7.30–7.45 (m, 8H), 7.65 (m, 2H), 10.56 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 39.5, 63.3, 103.4, 125.7, 126.5, 128.3, 129.1, 129.2, 129.8, 133.9, 134.1, 145.0, 151.2. APCI MS: 290 (MH^+). Anal. calcd. for $C_{17}H_{15}N_5$ C 70.57, H 5.23, N 24.20. Found C 70.80, H 5.17, N 24.59.

6',7',8',9'-Tetrahydro-4'*H*-spiro(cyclohexane-1,5'-[1,2,4]triazolo[1,5-*a*]quinazoline) 3ba. Yield 40%. Mp 225 °C.^1H NMR (500 MHz, DMSO-d_6), δ: 1.15 (m, 1H), 1.45 (m, 2H), 1.58–1.76 (m, 10H), 2.09 (m, 2H), 2.44 (m, 2H), 3.12 (m, 1H), 7.19 (br. s, 1H), 7.40 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 19.9, 21.6, 22.7, 23.2, 23.7, 25.3, 33.9, 56.8, 118.0, 127.2, 149.3, 152.7. APCI MS: 245 (MH^+). Anal. calcd. for $C_{14}H_{20}N_4$ C 68.82, H 8.25, N 22.93. Found C 69.06, H 8.44, N 23.27.

2'-(Trifluoromethyl)-6',7',8',9'-tetrahydro-4'*H*-spiro(cyclohexane-1,5'-[1,2,4]triazolo[1,5-*a*]quinazoline) 3bb. Yield 35%. Mp 158 °C. ^1H NMR (500 MHz, DMSO-d_6), δ: 1.12 (m, 1H), 1.44 (m, 2H), 1.59–1.72 (m, 10H), 2.07 (m, 2H), 2.41 (m, 2H), 3.34 (m, 1H), 7.98 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 19.8, 21.4, 22.5, 23.2, 23.4, 25.1, 34.0, 57.3, 120.1 (q, J = 269.3 Hz), 120.4, 126.8, 149.8 (q, J = 37.4 Hz), 153.6. APCI MS: 313 (MH^+). Anal. calcd. for $C_{15}H_{19}F_3N_4$ C 57.68, H 6.13, N 17.94. Found C 57.91, H 5.88, N 17.92.

Scheme 3



6',7',8',9'-Tetrahydro-4'*H*-spiro(cyclohexane-1,5'-tetrazolo [1,5-*a*]quinazoline) 3bc. Yield 46%. For spectral and physical data, see Ref. 29.

7-*tert*-Butyl-tetrazolo[1,5-*a*]pyrimidine 5. Yield 76%. Mp 164 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ: 1.41 (s, 9H), 7.76 (d, 2H, J = 7.3 Hz), 9.65 (d, 2H, J = 7.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 29.2, 40.8, 111.5, 134.8, 154.4, 179.9. APCI MS: 178 (MH^+). Anal. calcd. for $C_8H_{11}N_5$ C 54.22, H 6.26, N 39.52. Found C 53.87, H 6.41, N 39.60.

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