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Chlorotrimethylsilane-promoted synthesis of 1,2,4-triazolopyrimidines from 3,5-diamino-1,2,4-triazoles and pentane-2,4-diones

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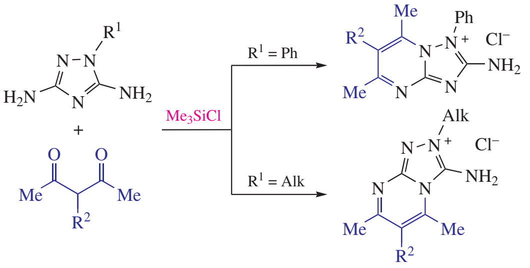
An efficient synthesis of 2-amino-1-R-[1,2,4]triazolo[1,5-*a*]pyrimidinium or 3-amino-2-R-[1,2,4]triazolo[4,3-*a*]pyrimidinium chloride derivatives by heterocyclization of 3,5-diamino-1-R-1,2,4-triazoles (R = Alk or Ar) with pentane-2,4-diones was developed. The process is promoted by chlorotrimethylsilane which plays the dual role of carbonyl-activating agent and water scavenger.



[1,2,4]Triazolopyrimidines of [1,5-*a*] and [4,3-*a*] annulation pattern have broad application in medicine, agrochemistry and coordination chemistry.[1–6] Practical importance of triazolopyrimidines can be illustrated by widely used vasodilator and anti-platelet agent Trapidil (Rocornal®),[7] herbicides flumetsulam, metosulam, and pyroxsulam,[8,9] fungicide ametoctradin (Initium®).[10] Numerous current researches in the field are devoted to developing new efficient medicaments and pesticides.[1–6,11–14]

Amino-substituted [1,2,4]triazolo[1,5-*a*]pyrimidines are currently considered as versatile multifunctional intermediates for the synthesis of various triazolopyrimidine derivatives, including polycyclic compounds.[15–18] Such aminotriazolopyrimidines are easily accessed by condensation of 3,5-diamino-1,2,4-triazole with 1,3-bielectrophiles.[19,20] However, analogous reactions of readily available 1-substituted 3,5-diamino-1,2,4-triazoles **1** containing two NH$_2$ groups of significantly different nucleophilicity[21] were less studied. It was reported that the condensation of compounds **1** with β-keto esters or 2-(alkoxymethylidene)malonates afforded 1- or 2-substituted 3(2)-amino[1,2,4]triazolo[4,3-*a*]pyrimidines depending on the reaction conditions.[22–24]

1,3-Diketones represent another class of versatile reagents for the synthesis of fused heterocycles,[25] however, published data on their reactions with compounds **1** are fragmentary and contradictory. It was reported that the condensation of 1-substituted 3,5-diamino-1,2,4-triazoles with 1,3-diketones could give differently annulated triazolopyrimidines: 2-amino-1-R-[1,2,4]triazolo[1,5-*a*]pyrimidines[26] and 3-amino-2-R-[1,2,4]triazolo[4,3-*a*]pyrimidines.[27] The reasons for the annulation difference were not clear. Moreover, under harsh reaction conditions (fusion of diaminotriazole salts with diketones at 130–150 °C),[26] 1-alkyl-3,5-diamino-1,2,4-triazoles suffered elimination of the group R to give N-dealkylated triazolo[1,5-*a*]pyrimidines, while under mild conditions (reflux in EtOH in the presence of HCl)[27] the yields of 3-amino-2-R-[1,2,4]triazolo[4,3-*a*]pyrimidines did not exceed 36%. Therefore, a task to ascertain factors affecting the annulation course of triazole and pyrimidine rings and to improve the synthetic procedures is topical.

Here, we report a new efficient approach to aminotriazolopyrimidines by the heterocyclization of 1-substituted 3,5-diamino-1,2,4-triazoles **1** with pentane-2,4-diones **2** promoted by chlorotrimethylsilane (TMSCl).

To ascertain the reaction pathway, a condensation of diaminotriazoles **1** with pentane-2,4-diones **2** in the absence of acidic catalysts was first studied. Upon reflux in ethanol, the condensation with participation of more nucleophilic 3-NH$_2$ group occurred to afford *Z*-enamino ketones **3a–g** (Scheme 1),[†] analogously to the reactions with other carbonyl compounds.[22–24]

Attempted cyclizations of compounds **3** in refluxing AcOH or DMF, or in melts at 100–150 °C, were unsuccessful and resulted in decomposition of the substrates. However, their short-time heating with HCl or HBr in ethanol led to aminotriazolopyrimidinium salts **4** or **5** in 32–64% yields (see Scheme 1, procedure i).[‡] When R^1 was Ph, the corresponding 1,2,4-triazolo[1,5-*a*]pyrimidines **4** were formed, and when R^1 was Alk, 1,2,4-triazolo[4,3-*a*]pyrimidines **5** were obtained. One-pot reaction between diaminotriazoles **1** and diketones **2** in ethanol in the presence of slight excess of HCl or HBr afforded the same compounds **4** or **5** in low to moderate yields (see Scheme 1, procedure ii).[‡] It is clear from

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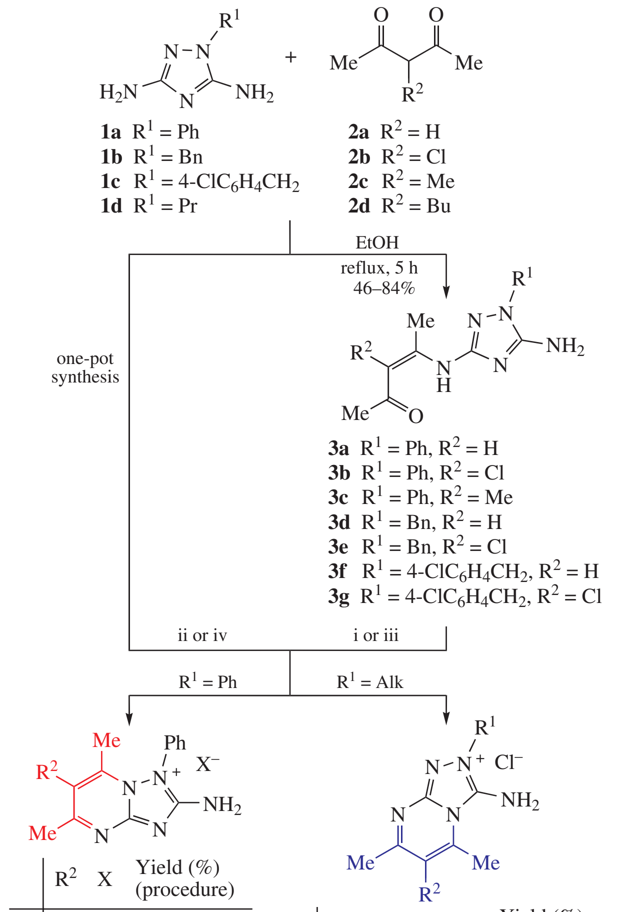
[†] *Compounds* **3a–g** (*general procedure*). A solution of diaminotriazole **1a–c** (6 mmol) and corresponding 1,3-diketone **2a–c** (7.8 mmol) was refluxed in EtOH (3 ml) for 5 h, then water (1 ml) was added. After cooling, the resulting precipitate was collected by filtration and recrystallized from ethanol.

*(3Z)-4-[(5-Amino-1-phenyl-1*H*-1,2,4-triazol-3-yl)amino]pent-3-en-2-one* **3a**. Yield 1.29 g (84%), colourless needles, mp 160–160.5 °C, $R_f = 0.45$. ^{1}H NMR, δ: 2.02 (s, 3H, Me), 2.32 (s, 3H, Me), 5.29 (s, 1H, C^{3}H), 6.62 (s, 2H, NH$_2$), 7.32–7.36 (m, 1H, Ph), 7.47–7.55 (m, 4H, Ph), 12.51 (s, 1H, NH). ^{13}C NMR, δ: 21.2 (Me), 29.3 (Me), 99.3 (C^3 of penten-2-one), 122.4, 126.7, 129.4, 137.1 (Ph), 153.9, 155.4 (triazole), 157.5 (C^4 of penten-2-one), 196.4 (CO). HRMS (ESI), *m*/*z*: 258.1351 [M + H]$^+$ (calc. for $C_{13}H_{16}N_5O$, *m*/*z*: 258.1349).

For characteristics of compounds **3b–g**, see Online Supplementary Materials.

[‡] For experimental details, see Online Supplementary Materials.



	R^2	X	Yield (%) (procedure)
4a	H	Br	64 (ii)
4b	H	Cl	32 (ii), 92 (iv)
4c	Cl	Br	37 (ii)
4d	Cl	Cl	32 (ii), 91 (iv)
4e	Me	Br	60 (ii)
4f	Me	Cl	54 (ii), 87 (iv)
4g	Bu	Br	49 (ii)

	R^1	R^2	Yield (%) (procedure)
5a	Bn	H	38 (ii), 82 (iv)
5b	Bn	Cl	42 (ii), 92 (iv)
5c	4-$ClC_6H_4CH_2$	H	36 (ii), 78 (iv)
5d	4-$ClC_6H_4CH_2$	Cl	34 (ii), 75 (iv)
5e	Pr	H	46 (ii), 72 (iv)

Scheme 1 *Reagents and conditions*: i, HCl or HBr in EtOH, reflux for 2 min; ii, HCl or HBr in MeCN, reflux for 30 min; iii and iv, TMSCl in MeCN, reflux for 2 min.

these results that acid catalysis is required at the stage of enamino ketone **3** heterocyclization.

The reaction is reversible at the both stages, that was confirmed by the separate experiments on the hydrolysis of compounds **4a** and **5a**,‡ and, apparently, the last stage is more sensitive to the presence of water. Therefore, scavenging water that releases in the course of the reaction would enhance the yields of triazolopyrimidines. We have revealed, that TMSCl in acetonitrile can be used as efficient promoter of the heterocyclization affording triazolopyrimidines **4** and **5** (as chlorides) in 84–98% isolated yields from enamino ketones **3** (see Scheme 1, procedure iii).‡ This synthesis can also be performed in a one-pot manner to provide 72–92% isolated yields by heating reactants **1** and **2** in MeCN, subsequent removing the solvent and forming water *in vacuo*, followed by heating the residue with TMSCl in fresh MeCN (see Scheme 1, procedure iv).§ Remarkably, addition of TMSCl after the formation of enamino ketones and removing water was more efficient than the simultaneous loading all the components. Chlorotrimethylsilane, apparently, serves as both carbonyl-activating agent and water scavenger.[28,29]

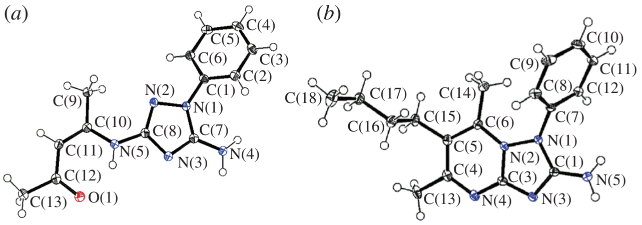


Figure 1 Molecular structures of compounds (*a*) **3a** and (*b*) **4g**. Displacement ellipsoids are drawn at the 50% probability level. Solvent molecules and Br^- (for **4g**) are omitted for clarity.

Structures of compounds **3**–**5** were unambiguously confirmed by ^1H and ^{13}C NMR spectra, including NOESY of **4a** and **5a**,**e**, and X-ray analysis of **3a** and **4g** (Figure 1).¶

Observed differences for the direction of the heterocyclization in the reactions of diaminotriazoles **1a** (R^1 = Ph) and **1b**–**d** (R^1 = Alk) can be explained by steric factors. DFT calculations were performed for model molecules of type **4** with Ph and Me groups as R^1 substituent (R^2 = H). The calculations revealed that [1,5-*a*]-isomers **4** are thermodynamically more stable than the [4,3-*a*]-isomers **5**.†† However, steric hindrance between the substituents R^1 and Me hampers the cyclization to form hypothetic isomers **4** with R^1 = Alk (Figure 1). As we reported, transformation of compounds **5a**,**b** (R^1 = Bn) into 2-amino[1,2,4]triazolo[1,5-*a*]pyrimidines was realized only with simultaneous elimination of Bn group within prolonged heating.[27] If R^1 is Ph (in compounds **4a**–**g**), the benzene ring turns perpendicularly to the triazole ring thereby decreasing steric hindrance and allowing

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§ *Compounds* **4b**,**d**,**f** *and* **5a**–**e** *(one-pot synthesis, procedure iv)*. A mixture of diaminotriazole **1a**–**d** (2.85 mmol), diketone **2a**–**c** (3.71 mmol), and MeCN (4 ml) was refluxed for 5 h, then volatiles were evaporated *in vacuo*. Dry MeCN (4 ml) was added to the obtained residue, the mixture was heated to dissolution, then TMSCl (0.621 g, 5.7 mmol) was added and reflux was continued for 2–3 min. The mixture was evaporated to a small volume (~2 ml), diluted with Et_2O (4 ml) and cooled to 0–5 °C. The product precipitated was filtered and recrystallized from MeCN.

*2-Amino-5,7-dimethyl-1-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidin-1-ium chloride* **4b**. Yield 725 mg (92%, procedure iv), colourless prisms, mp 214–216 °C. ^1H NMR, δ: 1.96 (s, 3H, Me), 2.60 (s, 3H, Me), 7.26 (s, 1H, CH), 7.68–7.85 (m, 5H, Ph), 8.45 (s, 2H, NH_2). ^{13}C NMR, δ: 17.7 (7-Me), 24.4 (5-Me), 113.6 (C^6), 130.2, 130.4, 132.3, 132.7 (Ph), 147.9 (C^7), 154.0, 159.9 (triazole), 170.5 (C^5). HRMS (ESI), *m/z*: 240.1241 $[M-Cl^-]^+$ (calc. for $C_{13}H_{14}N_5$, *m/z*: 240.1244).

*3-Amino-5,7-dimethyl-2-propyl[1,2,4]triazolo[4,3-*a*]pyrimidin-2-ium chloride* **5e**. Yield 496 mg (72%, procedure iv), colourless plates, mp 208–210 °C. ^1H NMR, δ: 0.94 (t, 3H, CH_2CH_2*Me*, *J* 7.4 Hz), 1.76–1.84 (m, 2H, CH_2), 2.45 (s, 3H, Me), 2.84 (s, 3H, Me), 4.30 (t, 2H, C^2H_2, *J* 7.1 Hz), 6.82 (s, 1H, C^6H), 8.69 (s, 2H, NH_2). ^{13}C NMR, δ: 10.5 (CH_2CH_2*Me*), 18.1 (5-Me), 21.3 (CH_2), 24.9 (7-Me), 49.5 (2-CH_2), 111.7 (C^6), 143.9 (C^3), 145.9 (C^5), 147.6 (C^{8a}), 169.5 (C^7). HRMS (ESI), *m/z*: 206.1399 $[M-Cl^-]^+$ (calc. for $C_{10}H_{16}N_5$, *m/z*: 206.1400).

For characteristics of compounds **4a**,**c**–**g** and **5a**–**d**, see Online Supplementary Materials.

¶ *Single crystal X-ray study.*

For **3a**: $C_{13}H_{15}N_5O\cdot H_2O$ (M = 275.32) at 100 K is monoclinic, space group $P2_1/n$, a = 7.3708(14), b = 21.614(4) and c = 8.4421(16) Å, β = = 97.968(3)°, V = 1331.9(4) Å^3, Z = 4, d_{calc} = 1.373 g cm^{-3}, μ = 0.097 mm^{-1}, $F(000)$ = 584, wR_2 = 0.0949 calculated on F^2_{hkl} [GOF = 1.018, R_1 = = 0.0352 calculated on F_{hkl} using 2576 reflections with $I > 2\sigma(I)$].

For **4g**: $C_{17}H_{22}N_5^+Br^-\cdot H_2O$ (M = 394.32) at 100 K is monoclinic, space group $P2_1/c$, a = 11.6895(7), b = 9.5654(6) and c = 16.1360(9) Å, β = 95.7650(10)°, V = 1795.12(19) Å^3, Z = 4, d_{calc} = 1.459 g cm^{-3}, μ = = 2.304 mm^{-1}, $F(000)$ = 816, wR_2 = 0.0602 calculated on F^2_{hkl} [GOF = = 1.023, R_1 = 0.0231 calculated on F_{hkl} using 4603 reflections with $I > 2\sigma(I)$].

For more details, see Online Supplementary Materials.

CCDC 1519403 and 1519405 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

†† For detailed results of quantum chemical calculations, see Online Supplementary Materials.

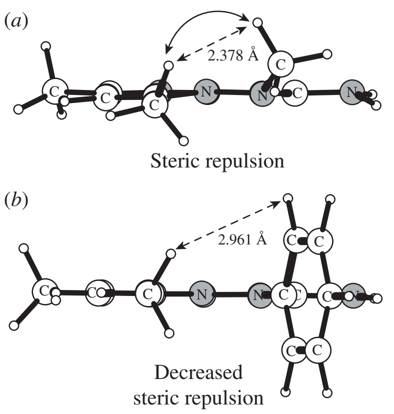

Figure 2 Optimized geometries of model molecules of type **4** with (*a*) R^1 = Me, R^2 = H and (*b*) R^1 = Ph, R^2 = H, B3LYP 6-311++G(2d,2p), aqueous solution (IEF-PCM).

isomers **4** to be formed (Figure 2). Remarkably, analogous influence of the R^1 group (Ph, Alk) on the selectivity of N^2 or N^4 alkylation of compounds **1** was observed.[21]

In conclusion, this study provides a new efficient approach to aminotriazolopyrimidines with various annulations of triazole and pyrimidine cycles and demonstrates the utility of 1-substituted 3,5-diamino-1,2,4-triazoles as versatile multifunctional reagents for the synthesis of condensed heterocycles.

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Online Supplementary Materials

Supplementary data associated with this article (synthetic procedures, detailed results of quantum chemical calculations and X-ray investigations, NMR and HRMS spectra) can be found in the online version at doi: 10.1016/j.mencom.2018.07.034.

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