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# A general approach toward the synthesis of 8-acylamido-pyrazolo[1,5-*a*]-1,3,5-triazines

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**Abstract**—An expedient synthesis of 8-acylamidopyrazolo[1,5-*a*]-1,3,5-triazines was developed by treating 8-amino-4-[*N*-(4-aminophenyl)-*N*-(methyl)amino]pyrazolo[1,5-*a*]-1,3,5-triazine with various acyl chlorides following by the displacement of the so-formed *N*-(methyl)-*N*-[4-(acylamido)phenyl]amino leaving group with various amines. Applications to high-throughput synthesis are suggested. © 2003 Elsevier Science Ltd. All rights reserved.

Pyrazolo[1,5-*a*]-1,3,5-triazines substituted in position 8 have attracted considerable interest from the medicinal chemist community over the past few years because of their wide range of biological activities.[1] Within our current research program on the synthesis and pharmacological evaluation of a variety of structurally related 9-substituted adenines as phosphodiesterase type 4 (PDE4) inhibitors[2] and $P2Y_1$-receptor antagonists[3] we became interested in bioisosteric replacement of the purine ring that would provide increased in vivo stability compared to the parent adenines **1**[3] and **3**.[2]

We have recently reported the synthesis of the 8-(2′-deoxy-β-D-ribofuranosyl)-2-methyl-4-(*N*-methylamino)-pyrazolo[1,5-*a*]-1,3,5-triazine-3′,5′-bisphosphate (**2**), a potent and selective $P2Y_1$-receptor antagonist, which possesses prolonged in vivo anti-aggregating properties compared to those of compound **1**.[4] In view of this promising result, we decided to apply the same synthetic strategy to the synthesis of C-analogs of 9-substituted $N^6$-methyladenines **3** as PDE4 inhibitors. To the best of our knowledge, there is only one example of 8-acylamidopyrazolo[1,5-*a*]-1,3,5-triazine, the 8-acetamido-4-(*N*-butylamino)-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**4**, Fig. 1), described in the literature.[5] This compound was obtained through a route that is not readily amenable to synthesis of $N^4$-substituted derivatives in a parallel fashion. The synthesis started from a $N^4$-pre-substituted pyrazolotriazine, which was nitrated selectively at position 8, followed by the reduction of the nitro group and a subsequent acylation.[5] Following this procedure would require additional steps to introduce substituents in position 4 resulting in a long synthetic route and losses in yields. These drawbacks

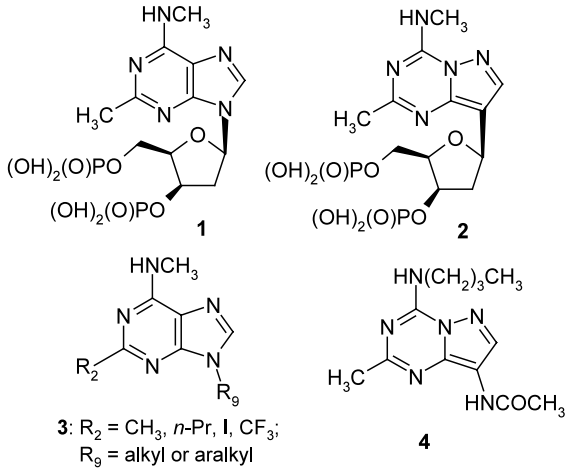


**Figure 1.**

*Keywords*: pyrazolo[1,5-*a*]-1,3,5-triazine; adenine; bioisoster; activating group.

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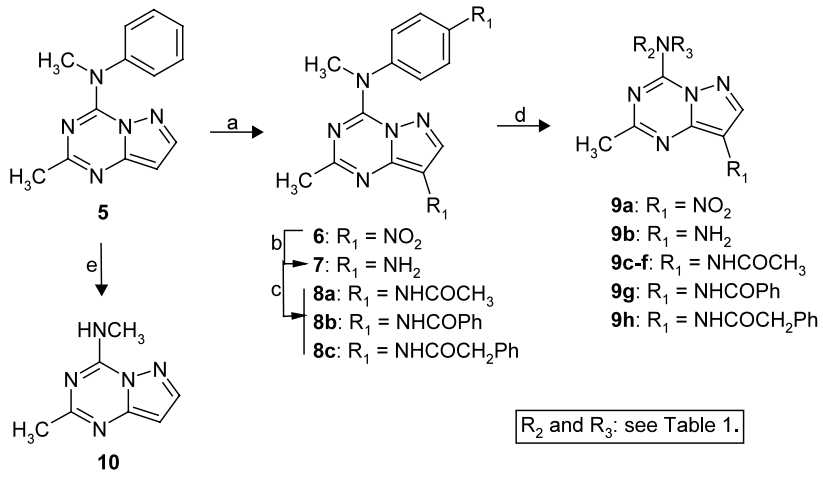


**Scheme 1.** *Reagents and conditions*: (a) $HNO_3$, 0°C, 10 min; (b) $H_2$–Pd/C, MeOH; (c) acyl chloride, TEA, $CH_2Cl_2$, 0°C; (d) $R_2R_3NH$, THF/EtOH, 80–110°C, 2–18 h, sealed tube; (e) $NH_2CH_3$, EtOH, 110°C, 10 h.

would limit the scope of this synthesis and point to a need for an improved method which permits an easy and rapid access to a large number of derivatives. Therefore, we sought to find an attractive methodology which employed an activating group at position 4 that could be readily displaced by various amines at the final step of the synthesis and that offers the necessary stability to permit the introduction of the acylamido moiety at position 8.

Recently, we have reported the use of the *N*-methyl-*N*-phenylamino (NMNPA) group as an optimized activating group, which possesses a number of favorable characteristics including stability, ease of handling and versatile reactivity.[4] Thanks to its low p$K_a$ (ca. 3.0), simple treatment of 4-(NMNPA)pyrazolo[1,5-*a*]-1,3,5-triazines (e.g. **5**) with an amine, either at reflux or in a sealed tube, results in a facile displacement of the NMNPA group, allowing for the synthesis of a variety of $N^4$-substituted analogs. Thus encouraged, we envision to use this activating group for the synthesis of 8-acylamidopyrazolotriazine **9c**–**h**.

This paper features the first general method for the synthesis of 8-acylamidopyrazolo[1,5-*a*]-1,3,5-triazines substituted at position 4 (Scheme 1), which is also applicable on both a parallel fashion and on a multigram scale reaction. This methodology is based on a di-acylation of the diamino derivative **7** followed by the displacement of the so-formed 4-acylated NMNPA group leading to the target final compounds **9c**–**h**.[6–8]

As outlined in Scheme 1, treatment of **5** with fuming nitric acid, afforded the dinitro compound **6** as the major product in 85% isolated yield after a single recrystallization from ethanol/ether.[6] Palladium-catalyzed hydrogenation afforded the diamino derivative **7**,[7] which was used as the starting material for the synthesis of 8-acylamidopyrazolotriazines **9c**–**h**. Acylation of **7** using 2.2 equiv. of acylchloride at 0°C, quantitatively afforded the target diacylamido derivatives **8a**–**c** (the total conversion of **7** to **8** was monitored by HPLC).[8]

Then, the displacement of the 4-substituted NMNPA leaving groups (intermediates **6**–**8**) was investigated using methylamine as a typical nucleophile amine (Table 1).

As seen previously with compound **5**,[4] the conversion of intermediates **6** and **8** to the targets compounds **9** required extended reaction times at room temperature presenting a drawback for an expedient preparation of 4-substituted derivatives, the reaction times could however be shortened to 2–18 h by running the reaction in a sealed tube at a temperature between 80 and 110°C.[8] As expected, the rate of the displacement of the NMNPA group appeared to be highly dependent on the substitutions at both position 8 and at the *para* position of the phenyl ring: the more electron poor the system, the faster it reacted. Thus, the order of reactivity was found to be $NO_2$>H>$NHCOR_2$>>>$NH_2$, consequently the displacement of the diamino derivative **7** was the most challenging, and even in a sealed tube at 110°C, we were unable to achieve significant conversion of **7** to the target compound **9b** (Table 1). In all other cases (compounds **5**, **6** and **8**), the NMNPA groups could be readily displaced with various amines and therefore opens up access to a wide variety of N-4

**Table 1.** Synthesis of 8-substituted pyrazolo[1,5-*a*]-1,3,5-triazines[6–8]

| Compound | $R_1$ | $R_2$ | $R_3$ | Yield (%)[a] |
|---|---|---|---|---|
| **10**[4] | H | $CH_3$ | H | 78[c] |
| **9a** | $NO_2$ | $CH_3$ | H | 86[b] |
| **9b** | $NH_2$ | $CH_3$ | H | 0[c] |
| **9c** | $NHCOCH_3$ | H | H | 83[c] |
| **9d** | $NHCOCH_3$ | $CH_3$ | H | 81[c] |
| **9e** | $NHCOCH_3$ | $CH_3$ | $CH_3$ | 86[c] |
| **9f** | $NHCOCH_3$ | $-(CH_2)_4-$ | | 91[c] |
| **9g** | NHCOPh | $CH_3$ | H | 92[c] |
| **9h** | $NHCOCH_2Ph$ | $CH_3$ | H | 88[c] |

[a] Yields of isolated products.
[b] Method A: $CH_3NH_2$, THF/EtOH, 80°C, 2 h, sealed tube.
[c] Method B: $R_2R_3NH$, THF/EtOH, 110°C, 5–18 h, sealed tube.

substituted 8-acylamido derivatives. No column chromatography was required and the final compounds **9a**, **9c**–**h** and **10** were generally obtained in high purity after a single recrystallization. Therefore, the process becomes even more attractive for parallel and large-scale applications when we found that it could be run at high concentration without sacrificing yield.

In summary, we have developed a rapid, practical and efficient procedure for the synthesis of 8-acylamido-pyrazolo[1,5-*a*]-1,3,5-triazine derivatives.[6–8] The impetus for this work was the easy access to the 8-amino-4-[*N*-(4-aminophenyl)-*N*-(methyl)amino]pyrazolo[1,5-*a*]-1,3,5-triazine **7**,[7] which was used as the starting material in a tandem of reactions involving: (i) the diacylation of both amino moieties with a acyl chloride and (ii) the displacement of the so-formed *N*-[4-(acylamido)phenyl]-*N*-(methyl)amino activating group with various amines at the end of the reaction that represents a concise and general route for the introduction of substitutions and functionalities at the 4-position.[8] Another main advantage for this procedure is the opening potentiality to use this strategy in a multi-gram scale synthesis or in a parallel fashion. This novel series of compounds are currently under biological evaluation for their phosphodiesterase inhibition properties.

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## References

1. (a) Lubbers, T.; Angehrn, P.; Gmunder, H.; Herzig, S.; Kulhanek, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 821–826; (b) He, L.; Gilligan, P. J.; Zaczek, R.; Fitzgerald, L. W.; McElroy, J.; Shen, H.-S.; Saye, J. A.; Kalin, N. H.; Shelton, S.; Christ, D.; Trainor, G.; Hartig, P. *J. Med. Chem.* **2000**, *43*, 449–456; (c) De Zwart, M.; Vollinga, R. C.; Beukers, M. W.; Sleegers, D. F.; Von Frijtag Drabbe, K.; Jacobien, K.; De Groote, M.; Ijzerman, A. P. *Drug Development Res.* **1999**, *48*, 95–103.
2. Bourguignon, J.-J.; Désaubry, L.; Raboisson, P.; Wermuth, C. G.; Lugnier, C. *J. Med. Chem.* **1997**, *40*, 1768–1770.
3. Raboisson, P.; Baurand, A.; Cazenave, J.-P.; Gachet, C.; Retat, M.; Spiess, B.; Bourguignon, J.-J. *J. Med. Chem.* **2002**, *45*, 962–972.
4. Raboisson, P.; Baurand, A.; Cazenave, J.-P.; Gachet, C.; Schultz, D.; Spiess, B.; Bourguignon, J.-J. *J. Org. Chem.* **2002**, *67*, 8063–8071.
5. Vogel, A.; Troxler, F. *Helv. Chim. Acta* **1975**, *58*, 761–771.
6. 2-Methyl-4-[*N*-methyl-*N*-(4-nitrophenyl)amino]-8-nitropyrazolo[1,5-*a*]-1,3,5-triazine (**6**). A solution of 2-methyl-4-(*N*-methyl-*N*-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazine **5** (2.39 g, 10 mmol) in fuming nitric acid (18 mL) was stirred at 0°C for 10 min. Then, the reaction mixture was diluted with cold water (150 mL). The yellow precipitate was filtered, then successively washed with cold water (2×10 mL), methanol (2×3 mL) and finally with diethyl ether. Recrystallization from ethanol and diethyl ether yielded compound **6** (2.7 g, 85%) as slightly yellow, crystalline solid. Mp 256°C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.74 (s, 3H, $CH_3$), 3.83 (s, 3H, $CH_3$), 7.38 (d, $J$=8.7 Hz, 2H, ArH), 8.28 (s, 1H, 7-H). $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ 26.7, 42.4, 121.8, 125.0, 127.8, 142.2, 146.4, 148.1, 149.6, 150.2, 169.5. MS: $(m/z)$=330 $(M+H)^+$. Anal. calcd for $C_{13}H_{11}N_7O_4$: C, 47.42; H, 3.37; N, 29.78. Found: C, 47.56; H, 3.54; N, 29.79.
7. 8-Amino-4-[*N*-(4-aminophenyl)-*N*-methylamino]pyrazolo-[1,5-*a*]-1,3,5-triazine (**7**). A mixture of **6** (600 mg, 1.8 mmol) and 10% Pd/C (100 mg) in absolute methanol (200 mL) was shaken in a hydrogenation apparatus at rt for 2 h. The catalyst was removed by filtration, washed with water and the filtrate was concentrated to dryness. Recrystallization from diethyl ether yielded **7** (333 mg, 68%) as yellow solid. Mp 166°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.54 (s, 3H, $CH_3$), 3.66 (s, 3H, $CH_3$), 6.68 (d, $J$=8.6 Hz, 2H, 2 ArH), 7.08 (d, $J$=8.6 Hz, 2H, 2 ArH), 7.50 (s, 1H, 7-H). MS: $(m/z)$=270 $(M+H)^+$. Anal. calcd for $C_{13}H_{15}N_7$: C, 57.98; H, 5.61; N, 36.41. Found: C, 57.88; H, 5.58; N, 36.63.
8. 8-Acetamido-2-methyl-4-(*N*-methylamino)pyrazolo[1,5-*a*]-1,3,5-triazine (**9d**). Acetyl chloride (47 μL, 0.66 mmol) was slowly added, at 0°C, to a stirred solution of **7** (80 mg, 0.30 mmol) in anhydrous dichloromethane (7 mL). Then, triethylamine (96 μL, 0.69 mmol) was added and stirring was continued for 5 min at 0°C. The reaction mixture was allowed to warm up to rt, diluted with ethyl acetate (15 mL), then washed with water (5 mL) and saturated sodium bicarbonate (2 mL), dried ($Na_2SO_4$) and concentrated to dryness under reduced pressure. The residue (crude **8b**) was dissolved in ethanol (5 mL) and a methylamine (1 M in EtOH, 2 mL) was added and the reaction mixture was stirred at 110°C in a sealed tube for 8 h. After cooling to rt, the mixture was taken up with ice-cooled water (10 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was dried ($Na_2SO_4$) and concentrated to dryness under reduced pressure. The residue was triturated in diethyl ether and filtered. Recrystallization from ethanol/diethyl ether afforded **9d** as colorless, crystalline solids (116 mg, 83%). Mp 241°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.07 (s, 3H, $CH_3$), 2.44 (s, 3H, $CH_3$), 3.02 (d, $J$=4.4 Hz, 3H, $CH_3$), 8.41 (s, 1H, 7-H), 8.68 (q, $J$=4.4 Hz, 1H, NH), 9.93 (s, 1H, NH). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 23.9, 25.0, 25.8, 42.6, 108.7, 120.6, 127.1, 137.2, 138.7, 140.6, 140.9, 148.9, 161.8, 168.0, 168.7. MS: $(m/z)$=221 $(M+H)^+$. Anal. calcd for $C_9H_{12}N_6O$: C, 49.08; H, 5.49; N, 38.16. Found: C, 49.27; H, 5.19; N, 38.02.