Pergamon

Tetrahedron Letters 43 (2002) 9501–9503

TETRAHEDRON LETTERS

Efficient synthesis of 8-substituted pyrazolo[1,5-*a*]-1,3,5-triazines by regioselective acylation

Pierre Raboisson,[a,*] Dominique Schultz,[a] Claire Lugnier[b] and Jean-Jacques Bourguignon[a]

[a]*Laboratoire de Pharmacochimie de la Communication Cellulaire (CNRS, UMR 7081), Faculté de Pharmacie, 74 route du Rhin, BP24, 67401 Illkirch Cedex, France*

[b]*Laboratoire de Pharmacologie et de Physico-Chimie des Interactions Cellulaires et Moléculaires (CNRS, UMR 7034), Faculté de Pharmacie, 74 route du Rhin, BP24, 67401 Illkirch Cedex, France*

Received 25 October 2002; accepted 30 October 2002

Abstract—An efficient two-step synthesis of 8-acylated pyrazolo[1,5-*a*]-1,3,5-triazines has been accomplished. The key strategic elements of this novel synthetic approach involve the use of the *N*-methyl-*N*-phenylamino activating group, which was easily obtained in high yield by treatment of the pyrazolotriazin-4-one with phosphorus oxychloride and dimethylaniline through high pressure reaction coupled with a regioselective acylation at position 8 followed by the subsequent displacement of the *N*-methyl-*N*-phenylamino group upon treatment with various amines.

Adenine derivatives substituted in position 9 (**1**, Fig. 1) were found in several biologically active molecules and have potent phosphodiesterase inhibition properties with high selectivity toward PDE4.[1] In our continuing search on the synthesis and pharmacological evaluation of a variety of structurally related compounds, our attention was focused on 8-substituted pyrazolo[1,5-*a*]-1,3,5-triazines (**2**, Fig. 1)[2a–c] as bioisosteres of **1**. Thus, regioselective acylation represent one of the most direct methods to introduce substitutions and functionalizations at position 8.

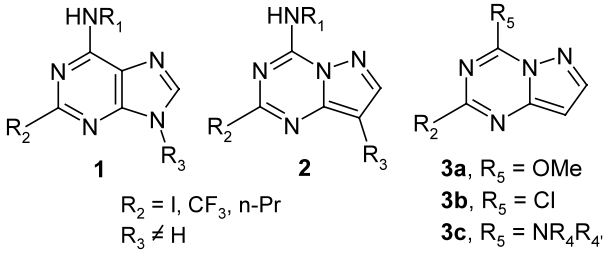


Figure 1.

Although electrophilic substitutions at position 8 of pyrazolotriazine (**3**) are well documented,[2a–c] attempts to acylate this bicycle using acyl chlorides or anhydrides under Friedel–Crafts general conditions failed to produce the desired products.[2a] Thus, the development of a generally applicable methodology to introduce acyl substituents in position 8 still represent a nice challenge in heterocyclic chemistry and merited further investigation.

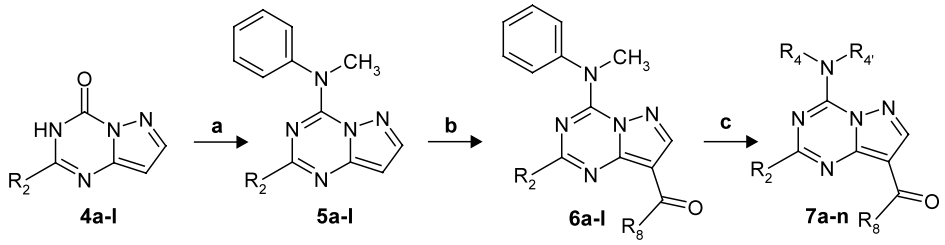
In this communication, we report the first general method for the synthesis of 8-acylated pyrazolo[1,5-*a*]-1,3,5-triazine using Tin(IV) chloride without solvent.

The nature of the substituent at position 4 appeared to be a crucial element in electrophilic substitution reactions on pyrazolo[1,5-*a*]-1,3,5-triazine because it can modify the electron density at position 8 and thus, regulate the rates of reactions. In addition, the optimal substituent would possess a sufficient stability under acylating conditions to avoid side products formations. Not surprisingly, attempts to acylate iminoether (**3a**) and iminochloride (**3b**) under Friedel–Crafts general conditions failed to undergo the desired adducts and led to a mixture of unseparable products. Similar results were obtained with the poorly soluble and 8-deactivated pyrazolotriazinones **4** (Scheme 1). Therefore, it was of great interest to develop a new activating group which would corroborate the low stability under acylating conditions of those previously reported.[2]

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

* Corresponding author. Present address: Department of Chemistry, 3-Dimensional Pharmaceuticals, Inc., 665 Stockton Drive, Exton, PA 19341, USA. E-mail: pierreraboisson@aol.com

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02456-5



Scheme 1. *Reagents and conditions*: (a) $POCl_3$, dimethylaniline, $CHCl_3$, 120°C, sealed tube; (b) R_8COCl, $SnCl_4$, 60°C; (c) $R_4R_{4'}NH$, EtOH, 100°C, sealed tube.

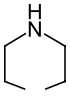
Table 1.

Compd[a]	R_2	R_8	Yields[b] (%)
6a	Me	Ph	85
6b	Et	Ph	76
6c	*n*-Pr	Ph	78
6d	*n*-Bu	Ph	64
6e	CH_3OCH_2	Ph	81
6f	2-Furyl	Ph	52
6g	MeS	Ph	49
6h	Me	4-(MeO)Ph	47
6i	Me	3-(CF_3)Ph	63
6j	Me	2-ClPh	36
6k	Me	EtO	41
6l	Me	$(Et)_2N$	43

[a] Conditions: PhCOCl, $SnCl_4$, 60°C.
[b] Unoptimized yields represent the result of a single experiment.

Recently, we have found that the 4-(*N*-methyl-*N*-phenylamino) group represents an optimized activating group, which was easily obtained in high yield by treatment of corresponding pyrazolotriazin-4-one **4** with phosphorus oxychloride and dimethylaniline through high-pressure reaction.[3] Indeed, this *N*-methyl-*N*-phenylamino group is readily displaced by various amines to afford the target compound.[3] Moreover, their high stability, makes the *N*-methyl-*N*-phenylamino derivatives **5** suitable candidates for acylating reactions. Thus, different experimental conditions using different Lewis acids and solvents in the presence of benzoyl chloride as a typical acid chloride were also investigated. Attempts to drive the reaction in presence of carbon disulfide, toluene, benzene or dichlorobenzene in presence of aluminum- or Tin(IV)-chloride at different temperatures were found inefficient, highlighted the poor nucleophilicity at the C-8 position. However, to our satisfaction, when the reaction was performed without solvent, in the presence of benzoyl- and Tin(IV)-chlorides, the target acylated compound **6a** was obtained in 85% isolated yield (Table 1).[4] Moreover, this reaction was generalized to other pyrazolotriazines **5** and other acylating agents. Results are summarized in Table 1. Although the reaction of **5** with various aromatic acyl chlorides afforded the expected 8-substituted derivatives **6** in acceptable yield (36–85%),[4] these conditions were not successfully generalized to the aliphatic

Table 2.

Compd	R_2	R_4	$R_{4'}$	R_8	Yields[a] (%)
7a	Me	H	H	Ph	67
7b	Me	Me	H	Ph	95
7c	Me	Me	Me	Ph	
7d	Me	Bn	H	Ph	63
7e	Me			Ph	53
7f	Me			Ph	78
7d	Et	Me	H	Ph	68
7e	*n*-Pr	Me	H	Ph	87
7f	*n*-Bu	Me	H	Ph	55
7g	CH_3OCH_2	Me	H	Ph	74
7h	2-Furyl	Me	H	Ph	56
7i	MeS	Me	H	Ph	75
7j	Me	Me	H	4-(MeO)Ph	40
7k	Me	Me	H	3-(CF_3)Ph	61
7l	Me	Me	H	2-ClPh	79
7m	Me	Me	H	EtO	69
7n	Me	Me	H	$(Et)_2N$	86

[a] Unoptimized yields represent the result of a single experiment.

acyl chlorides or anhydrides. Interestingly, oxalyl chloride permitted, after treatment at the end of the reaction with ethanol or diethylamine, the access to the 8-ethoxycarbonyl and diethylaminocarbonyl derivatives (**6k** and **6l**, respectively). Finally, the *N*-methyl-*N*-phenylamino group was easily displaced with various amines, leading to N^4-substituted derivatives **7**.[5] The final products are grouped in Table 2.

In summary, we have developed a rapid, practical and regioselective acylation of pyrazolo[1,5-*a*]-1,3,5-triazines as 9-substituted adenine bioisosteres. The impetus for this work is the easy access to the 4-(*N*-methyl-*N*-phenylamino) derivatives (**5**), obtained by treatment of the corresponding pyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**4**) with phosphorus oxychloride and dimethylaniline. Another main advantage of this method is the regioselectivity of the acylation at position 8 that eliminated the need for regioisomer separation and thus, significantly enhances the convenience and efficiency of this synthetic approach. Finally, the displacement of the *N*-methyl-*N*-phenylamino group at the end of the reaction represent a concise and general method to introduce substitutions and functionalities under position 4. However, this methodology appeared to be limited to aromatic and oxalyl chlorides. This novel series of compounds are currently under biological evaluation for their phosphodiesterase inhibition properties.

Acknowledgements

Support from the Louis Pasteur University is gratefully acknowledged.

References

1. Bourguignon, J.-J.; Désaubry, L.; Raboisson, P.; Wermuth, C. G.; Lugnier, C. *J. Med. Chem.* **1997**, *40*, 1768–1770.
2. (a) Vogel, A.; Troxier, F. *Helv. Chim. Acta* **1975**, *58*, 761–771; (b) Senga, K.; O'Brien, D. E.; Scholten, M. B.; Novinson, T.; Miller, J. P.; Robins, R. K. *J. Med. Chem.* **1982**, *25*, 243–249; (c) Zhang, H.-C.; Brakta, M.; Davies, G. D., Jr. *Nucleosides Nucleotides* **1995**, *14*, 105–116.
3. Raboisson, P.; Schultz, D.; Baurand, A.; Cazenave, J.-P.; Gachet, C.; Spiess, B.; Bourguignon, J.-J. *J. Org. Chem.* **2002**, *67*, 8063–8071.
4. *Typical procedure*: 8-benzoyl-2-methyl-4-(*N*-methyl-*N*-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazine **6a**: To a solution of 2-methyl-4-(*N*-methyl-*N*-phenylamino) pyrazolo-[1,5-*a*]-1,3,5-triazine **5a** (227 mg, 1.0 mmol) in benzoyl chloride (580 μL, 5.0 mmol) was slowly added Tin(IV)-chloride (588 μL, 5 mmol) under an argon atmosphere. The mixture was stirred at 60°C for 12 h, concentrated under reduced pressure, then diluted with cold water (20 mL) and extracted three times with ethyl acetate (30 mL). Organic layers were subsequently dried (Na_2SO_4) and concentrated to dryness under reduced pressure. Chromatography on silica (AcOEt/hexane, 1:2) afforded compounds **6a** as a colorless solid (293 mg, 85%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.68 (s, 3H, 2-CH_3), 3.79 (s, 3H, NCH_3), 7.20–7.60 (m, 8H, 8 ArH), 7.84–7.90 (m, 2H, 2 ArH), 8.05 (s, 1H, 7-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.6, 42.8, 108.8, 126.6, 127.9, 128.5, 129.6, 129.7, 132.3, 139.6, 144.8, 147.7, 149.6, 152.6, 167.3, 188.7. EIMS *m*/*z* 344 $(M+H)^+$. Anal. calcd for $C_{20}H_{17}N_5O$: C, 69.96; H, 4.99; N, 20.39. Found: C, 70.01; H, 5.10; N, 20.52.
5. A solution of **6a** (300 mg, 0.87 mmol), methylamine (2 M, 2.0 mL, 4.0 mmol) in ethanol (10 mL) was stirring at 80°C in a sealed tube for 6 h. After cooling the solvent was evaporated under reduced pressure. The crude reaction product was purified by column chromatography on silica gel (AcOEt/hexane, 1:1). Recrystallization from ethanol and diethyl ether yielded compound **7a** (212 mg, 91%) as colorless crystals: mp: 198°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.62 (s, 3H, 2-CH_3), 3.27 (d, $J=3.34$, 3H, NCH_3), 6.64 (q, $J=3.34$, 1H, NH), 7.46–761 (m, 3H, 3 ArH), 7.90–7.93 (m, 2H, 2 ArH), 8.32 (s, 1H, 7-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.7, 27.9, 110.4, 128.6, 129.8, 132.6, 139.3, 148.4, 149.5, 149.6, 168.3, 188.7. EIMS *m*/*z* 268 $(M+H)^+$. Anal. calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 63.01; H, 5.07; N, 26.19.