New Polynitrogen Materials Based on Fused 1,2,4-Triazines

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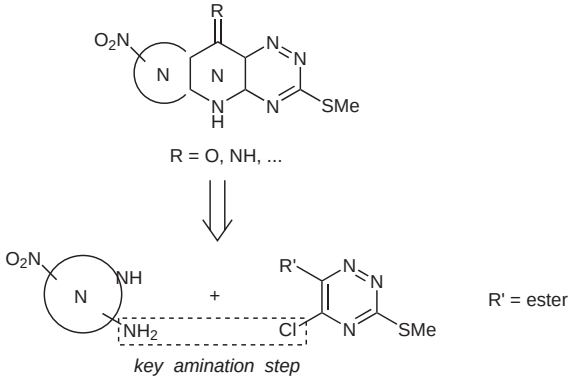
Abstract: The synthesis of several novel polynitrogen materials based on fused 1,2,4-triazines is described. A powerful palladium-catalyzed N-heteroarylation strategy followed by a cyclization provides a straightforward one-pot reaction to these tricyclic materials.

Key words: N-arylation reactions, palladium, energetic materials, 1,2,4-triazines

The development of novel heterocyclic materials finds applications in a wide variety of fields including propellants and explosives. In the course of our study of new performant insensitive energetic molecules, our laboratory was interested in the synthesis of novel heterocyclic materials such as polynitrogen tricyclic skeletons to significantly increase the stability of the final compounds. To our knowledge, the effects of polynitro functionalization on mono- or bicyclic rings often gives rise to unstable and very sensitive compounds.

Our interest in developing tricyclic species was to generate more stable compounds.[1] Indeed, the electron delocalization and the distribution of energetic functions should be favorable to stabilize the final structures. To generate very interesting energetic properties, materials have to satisfy two major criteria: a per volume ratio greater than 1.9 g cm^{-3} and a high heat of formation (ideally positive).

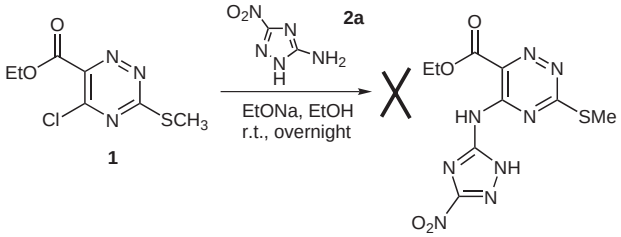


Scheme 1 Access to tricyclic functionalized skeletons

These parameters have a fundamental impact on the pressure and the speed of detonations. Therefore, nitro functionalized and polynitrogen tricyclic fused structures were designed to increase both of these parameters.

To access tricyclic structures, the ethyl 5-chloro-3-methylsulfanyl-1,2,4-triazine-6-carboxylate (**1**) seemed to be an interesting starting material due to its two substituents in the 5- and 6-position. Indeed the chloride atom could be displaced in a key amination step and the further cyclization should occur on an ester moiety (Scheme 1). 1,2,4-Triazine derivatives are good energetic candidates because they possess high positive heats of formation and high crystalline densities. Furthermore, this heterocycle has received a high degree of attention in the literature due to its synthetic potential and unique reactivity.[2]

In 1980, Benichon,[3a] followed by Huang,[3b] Warner[3c] and Pamukcu,[3d] described the formation of azapteridines by reaction of **1** with different amidines under basic conditions. Unfortunately, in our case, by using the 3-amino-5-nitro-1,2,4-triazole (ANT, an interesting energetic precursor, **2a**) and sodium ethoxide in ethanol, no displacement of the chlorine atom was observed and the starting material was completely recovered (Scheme 2).



Scheme 2 Reactivity of ANT **2a** with **1** under basic conditions

The low level of nucleophilicity displayed by heteroaromatic amines is not sufficient to allow substitution on triazines. In few previous reports on the reactivity of electron-poor heteroaromatic amines, difficulty was encountered in preparing *N*-heteroarylamino-1,2,4-triazines.[4] Based on our recent study,[5] we speculated that a palladium-catalyzed N-heteroarylation would be the solution to achieve the key step of the synthetic strategy (Scheme 1).[6] A single product was formed and isolated as a yellow oil as a result of the coupling reaction between the 3-amino-5-nitro-1,2,4-triazole (**2a**) with **1** followed by in situ cyclization. Nevertheless, at this stage, it was not clear

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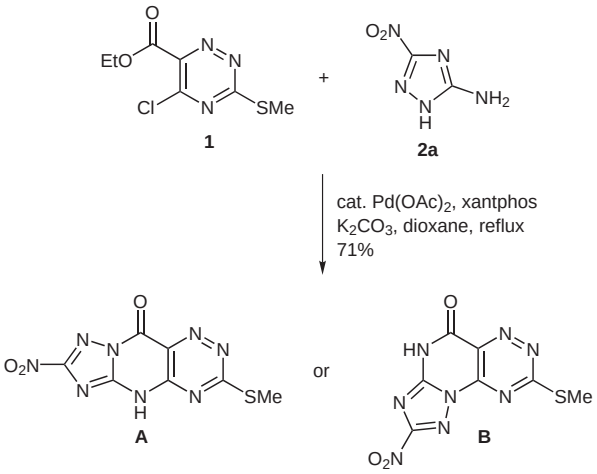
which of the two possible regioisomers were formed, **A** or **B** (Scheme 3). When the reaction was performed without palladium catalyst and base, or at room temperature, the cross-coupling reaction failed.

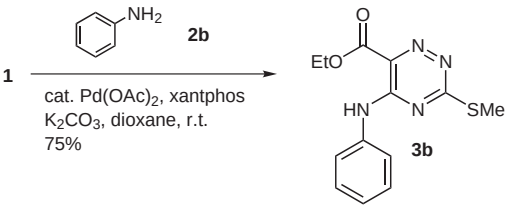


Scheme 3 Two possible regioisomers **A** or **B**

Owing to the lack of hydrogens on the final compound (**A** or **B**) and our inability in accessing suitable single crystals, we used ^{15}N NMR analysis to confirm the structure of this novel polynitrogen compound. Eight nitrogen environments were observed including the characteristic signals for NO_2 and NH at $\delta = 12$ ppm and $\delta = -258$ ppm, respectively.[7] Both ^{1}H NMR and ^{13}C NMR spectra confirmed the disappearance of the ethyl chain. Moreover, mass spectrometry revealed no presence of a chloro group. The presence of the amino and carbonyl function was confirmed by IR analysis. Therefore, in an attempt to determine the exact structure of the final product (Scheme 3) we wondered if (i) the substitution of the chlorine atom was carried out by the NH or NH_2 of the azole moiety, and (ii) if the first step is the amide formation or N-arylation.

According to our previous report,[5] in amino–azaheterocycle bearing at least two nucleophilic nitrogens, the primary amine was the most reactive. Consequently, we assumed that in the present case the exocyclic amine reacts first. However, we were reluctant to make a definitive structural assignment without being sure that the coupling reaction constituted the first step of the cyclization. For this purpose, we compared the reactivity of the ester and chloro functions of compound **1** using a substrate bearing only one nucleophilic amine. As a model, aniline **2b** was reacted with compound **1**. The reaction was found to take place at position 5 of the triazine ring to give compound **3b** in 75% yield (Scheme 4). This result shows that the palladium-catalyzed N-arylation reaction occurs before the addition–elimination reaction with the ester function.

Therefore, this 'one-pot' cyclization mechanism occurs first by the N-arylation reaction followed by the cyclization with the ester moiety, leading to the only regioisomer



Scheme 4 Reactivity of aniline **2b** with **1** in Pd-catalyzed conditions

A (Table 1, run 1). This outcome is consistent with the report of Huang,[3b] reporting that the reaction of compound **1** with ammonia led to substitution of chloride without reacting with the ester function. It is noteworthy that our structural assignment is based on the fact that N-alkylation of triazole is described to occur at N(1) rather than N(4).[8]

Table 1 N-Arylations[9] with Various Heteroarylamines **2a**,**c**–**h**

Run	Amine	Product[a]	Yield (%)[b,c]
1	**2a**	**3a**	71
2	**2c**	**3c**	65
3	**2d**	**3d**	62
4	**2e**	**3e**	67
5	**2f**	**3f**	64
6	**2g**	**3g**	68
7	**2h**	**3h**	59

[a] Yield of pure, isolated compound.
[b] The remaining material was constituted of degradation compounds.

These first optimized conditions[5] were used for a comparative study with different heteroarylamines (Table 1).[9] Various five-membered heterocycles were reacted with triazine **1** and after 'one-pot' cyclization, the corresponding tricyclic fused heterocycles were isolated in 62% to 71% isolated yield (Table 1, runs 1–6). Six-membered ring amines also react. For example, 2-aminopyrimidine (**2h**) was converted to compound **3h** in 59% yield (Table 1, run 7).

We have demonstrated that palladium-catalyzed N-heteroarylation conditions can be used with ethyl 5-chloro-3-methylsulfanyl-1,2,4-triazine-6-carboxylate (**1**) and various electron-poor amines **2a**–**h**. Our optimized coupling conditions were successfully applied to the 'one-pot' synthesis of compounds **3a**,**c**–**h**, in good yields. Current efforts are directed towards the reactivity of the methylsulfanyl group in order to increase the energetic properties of the final products. These studies will be communicated in due course.

References and Notes

(1) (a) Millar, R. W.; Philbin, S. P.; Claridge, R. P.; Hamid, J. *Propellants, Explos., Pyrotech.* **2004**, 81. (b) Sikder, A. K.; Sikder, N. *J. Hazard. Mater.* **2004**, *A112*, 1. (c) Singh, G.; Singh Kapoor, I. P. *J. Hazard. Mater.* **1999**, *A68*, 155. (d) Chapman, R. D.; Wilson, W. S. *Thermochim. Acta* **2002**, *384*, 229.

(2) For C–C bond formation, see: (a) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Synlett* **2002**, 447. (b) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803. (c) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Synthesis* **2004**, 2893. (d) For general chemistry, see: Neunhoffer, H. *Comprehensive Chemistry II*, Vol. 6; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. W., Eds.; Pergamon Press: Oxford UK, **1996**, 507. For inverse-electron-demand Diels–Alder reaction, see: (e) Lipinska, T. *Tetrahedron Lett.* **2002**, *43*, 9565. (f) Lahue, B.; Wan, Z.-K.; Snyder, J. K. *J. Org. Chem.* **2003**, *68*, 4345. (g) Lahue, B. R.; Lo, S.-M.; Wan, Z.-K.; Woo, G. H. C.; Snyder, J. K. *J. Org. Chem.* **2004**, *69*, 7171. (h) Branowska, D. *Synthesis* **2003**, 2096. (i) Bilbao, E. R.; Alvarado, M.; Masguer, C. F.; Ravina, E. *Tetrahedron Lett.* **2002**, *43*, 3551 . For fused 1,2,4-triazine derivatives, see: (j) Garnier, E.; Guillard, J.; Pasquinet, E.; Suzenet, F.; Poullain, D.; Jarry, C.; Léger, J.-M.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 4595. (k) Mojzych, M.; Rykowski, A. *Heterocycles* **2004**, *63*, 1829. (l) Chupakhin, O. N.; Rusinov, G. L.; Beresnev, D. G.; Charushin, V. N.; Neunhoeffer, H. *J. Heterocycl. Chem.* **2001**, *38*, 901. (m) Nagai, S.-I.; Miyachi, T.; Nakane, T.; Ueda, T.; Uozumi, Y. *J. Heterocycl. Chem.* **2001**, *38*, 379.

(3) (a) Pesson, M.; Antoine, M.; Benichon, J.-L.; de Lajudie, P.; Horvath, E.; Leriche, B.; Patte, S. *Eur. J. Med. Chem.* **1980**, *15*, 269. (b) Huang, J. J. *J. Org. Chem.* **1985**, *50*, 2293. (c) Taylor, E. C.; McDaniel, K. F.; Warner, J. C. *Tetrahedron Lett.* **1987**, *28*, 1977. (d) Piazza, G. A.; Pamukcu, R. Am. Pat. Appl. US6060477, **2000**; *Chem. Abstr.* **2000**, *132*, 321870.

(4) (a) Jonckers, T. H. M.; Maes, B. U. W.; Lemière, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027. (b) Košmrlj, J.; Maes, B. U. W.; Lemière, G. L. F.; Haemers, A. *Synlett* **2000**, 1581. (c) De Riccardis, F.; Johnson, F. *Org. Lett.* **2000**, *2*, 293. (d) Schoffers, E.; Olsen, P. D.; Means, J. C. *Org. Lett.* **2001**, *3*, 4221. (e) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481.

(5) Garnier, E.; Audoux, J.; Pasquinet, E.; Suzenet, F.; Poullain, D.; Lebret, B.; Guillaumet, G. *J. Org. Chem.* **2004**, *69*, 7809.

(6) For reviews about metal-catalyzed C–N bond formation, see: (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) Baranano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287. (c) Muci, A. R.; Buchwald, S. L. *Cross-Coupling Reactions*, In *Topics in Current Chemistry*, Vol. 219; Springer-Verlag: Berlin / Heideberg, **2002**, 131. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

(7) For chemical shift assignment, see: Martin, M. L.; Gouesnard, J.-P. In *^{15}N-NMR Spectrometry*; Diehl, P.; Fluck, E.; Kosfeld, R., Eds.; Springer-Verlag: New York, **1981**, 4.

(8) Garratt, P. J. *Comprehensive Chemistry II*, Vol. 4; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. W., Eds.; Pergamon Press: Oxford UK, **1996**, 127.

(9) **Typical Procedure for the Pd-Catalyzed N-Arylation Cyclization.**
A three-necked flask was flushed with N_2 and charged with xantphos (20 mol%) and dry dioxane (5 mL). After degassing, $Pd(OAc)_2$ (10 mol%) was added and the mixture was stirred under N_2 for 10 min. In another three-necked round-bottom flask, compound **1** (0.100 g, 1.0 equiv), heteroarylamine (1.2 equiv) and K_2CO_3 (20 equiv) were poured into dry dioxane (7 mL). Then, the $Pd(OAc)_2$/xantphos solution was added via cannula. The resulting mixture was subsequently heated to reflux and vigorously stirred until **1** has disappeared. After cooling down, the solid material was filtered off and washed with CH_2Cl_2 (20 mL) and MeOH (20 mL). The solvent was evaporated and the resulting crude product was purified by flash column chromatography using CH_2Cl_2–MeOH (99:1 v/v) as eluent.
Characterization of Compounds 3a and 3b.
Compound **3a**: ^{1}H NMR (200 MHz, DMSO): δ = 2.10 (s, 3 H, CH_3), 11.97 (br s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, DMSO): δ = 13.1 (CH_3), 144.8 (C_{10a}), 153.7 (C_{5a}), 154.1 (C_{10}), 154.6 (C_{4a}), 165.5 (C_7), 178.1 (C_3) ppm. ^{15}N NMR (30 MHz, DMSO): δ = –296, –258 (NH), –133, –154, –54, –49, 5, 12 (NO_2) ppm. IR: ν = 3223, 2975, 1652, 1521, 1352, 1023 cm^{-1}. MS: *m/z* = 281 [M + 1]. Anal. Calcd for $C_7H_4N_8O_3S$: C, 30.00; H, 1.44; N, 39.99. Found: C, 30.11; H, 1.48; N, 40.05.
Compound **3b**: ^{1}H NMR (200 MHz, DMSO): δ = 1.30 (t, *J* = 8.1 Hz, 3 H, CH_3), 2.37 (s, 3 H, SCH_3), 4.14 (q, *J* = 8.1 Hz, 2 H, CH_2), 7.03 (dd, $J_{2',4'}$ = 1.1 Hz, $J_{3',4'}$ = 7.4 Hz, 1 H, $H_{4'}$), 7.43 (dd, $J_{2',3'}$ = 7.9 Hz, $J_{3',4'}$ = 7.4 Hz, 2 H, $H_{3'}$ and $H_{5'}$), 7.93 (dd, $J_{2',4'}$ = 1.1 Hz, $J_{2',3'}$ = 7.9 Hz, 2 H, $H_{2'}$ and $H_{6'}$), 11.43 (br s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, DMSO): δ = 12.1 (CH_3), 14.07 (CH_3), 62.0 (CH_2), 122.9 ($C_{4'}$), 123.5 ($C_{2'}$ and $C_{6'}$), 126.6 ($C_{3'}$ and $C_{5'}$), 140.5 (C_6), 149.4 ($C_{1'}$), 155.6 (C_5), 163.8 (C=O), 188.1 (C_3) ppm. IR: ν = 3188, 2932, 1726, 1663 cm^{-1}. MS: *m/z* = 291 [M + 1]; mp 85–87 °C. Anal. Calcd for $C_{13}H_{14}N_4O_2S$: C, 53.78; H, 4.86; N, 19.30. Found: C, 54.01; H, 4.54; N, 19.12.