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A novel method for the preparation of *N*,*N*′-disubstituted-*N*″-nitroguanidines, including a practical synthesis of the neonicotinoid insecticide clothianidin

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Abstract

A novel method is described for the synthesis of *N*,*N*′-disubstituted-*N*″-nitroguanidines **3** via 2-nitroimino-hexahydro-1,3,5-triazine intermediates **12**, allowing the introduction of the heteroarylmethyl group either from a heteroarylmethyl amine **9** or a heteroarylmethyl chloride **14**, respectively. This method enables an efficient synthesis of the neonicotinoid insecticide clothianidin (**3b**) in four steps from *S*-methyl-*N*-nitro-isothiourea (**10**). © 2000 Elsevier Science Ltd. All rights reserved.

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Neonicotinoids **1** have attracted the attention of many research groups in industry and academia because of their outstanding insecticidal activity.[1] In the course of our research in this field, we have synthesised acyclic nitroguanidines **2**.[2,3] Among these compounds *N*-(6-chloro-pyridin-3-ylmethyl)-*N*′-methyl-*N*″-nitroguanidine (**3a**) and *N*-(2-chloro-thiazol-5-ylmethyl)-*N*′-methyl-*N*″-nitroguanidine (**3b**) (Scheme 2) were found to possess exceptional activity against a wide range of commercially important pests such as aphids, whiteflies, hoppers and some *Coleopteran* and *Lepidopteran* pests.[2] Takeda Chemical Industries, Ltd., has selected the neonicotinoid **3b** for development.[4] The compound is currently tested in extensive field trials under the code number TI-435 or its proposed common name clothianidin (ISO draft proposal). We report herein a novel method for the preparation of *N*,*N*′-disubstituted N″-nitroguanidines from *S*-methyl-*N*-nitroisothiourea (**10**), and its application in an efficient synthesis of compounds **3a** and **3b**.

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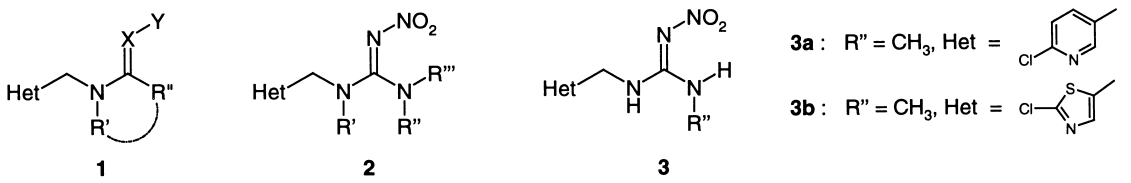
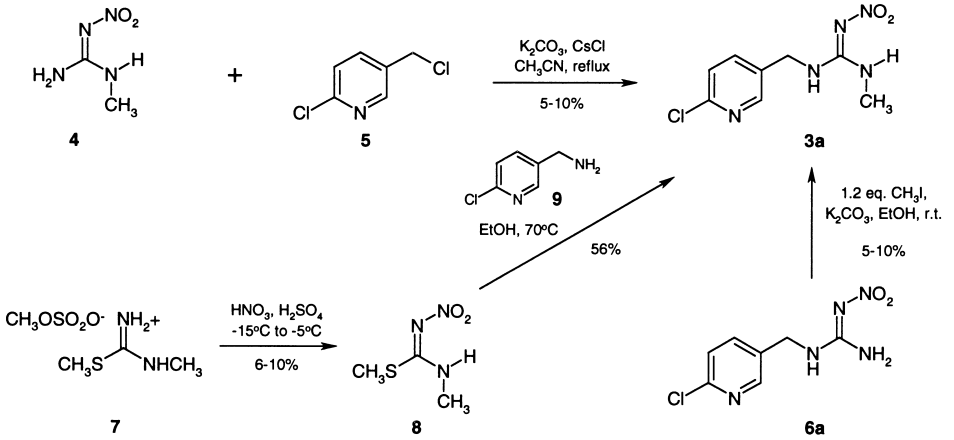
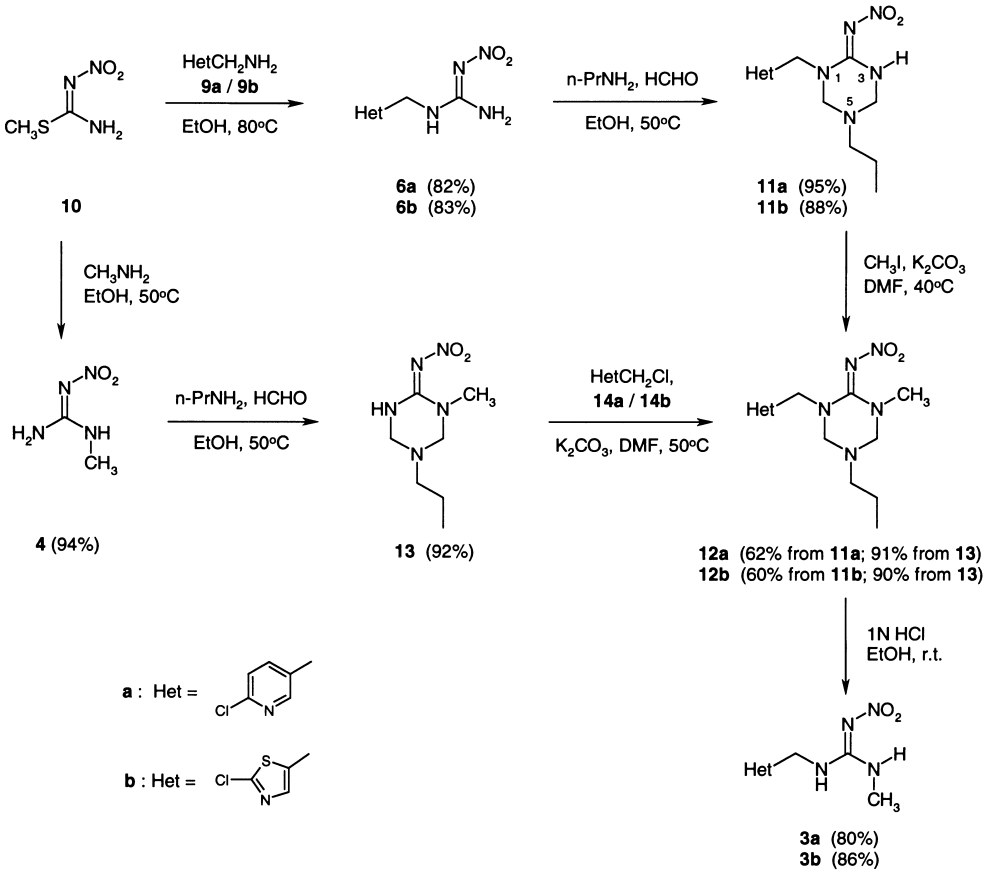


At the start of our research, no practical method for the preparation of *N*,*N*′-disubstituted-*N*″-nitroguanidines, such as compounds **3**, was available. Our initial efforts towards the synthesis of **3a** (Scheme 1) involved selective alkylation of monosubstituted nitroguanidines. Thus, treatment of *N*-methyl-*N*′-nitroguanidine (**4**)[5] with 6-chloro-pyridin-3-ylmethyl chloride (**5**) in dimethylformamide (DMF) or acetonitrile (CH_3CN), using potassium carbonate (K_2CO_3) or sodium hydride (NaH) as a base, afforded complex mixtures from which the desired product **3a** could be isolated in very low yields (5–10%). Similar results were obtained when *N*-(6-chloro-pyridin-3-ylmethyl)-*N*′-nitroguanidine (**6a**)[5] was alkylated with methyl iodide. In a further approach, the nitroguanidine **3a** was prepared in a two-step synthesis starting from *N*,*S*-dimethylisothiouronium methosulfate (**7**). Nitration of **7**, formed by treatment of *N*-methylthiourea with dimethylsulfate, in fuming nitric acid and concentrated sulfuric acid at –15°C to –5°C afforded the nitroisothiourea **8**, but the yields were only 6–10%. All attempts to improve this yield by variation of the nitration conditions were unsuccessful. The conversion of **8** to **3a** proceeded smoothly in 56% yield. Although compound **3a** and several analogues could be prepared and submitted for biological evaluation via these routes, a practical method for the synthesis of *N*,*N*′-disubstituted-*N*″-nitroguanidines was clearly required.



Scheme 1. Initial syntheses of **3a**

After some experimentation, a novel procedure was discovered which is widely applicable and which produces *N*,*N*′-disubstituted-*N*″-nitroguanidines in excellent yields.[6] This method is illustrated in Scheme 2 and allows the introduction of the heteroarylmethyl group either from a heteroarylmethyl amine or a heteroarylmethyl chloride, respectively. Thus, treatment of the readily available *S*-methyl-*N*-nitroisothiourea (**10**)[7] with amines **9** in EtOH at 80°C afforded the monosubstituted nitroguanidines **6** in excellent yields,[8] which could then be converted to the



Scheme 2. Novel method for the synthesis of *N*,*N*′-disubstituted-*N*″-nitroguanidines

nitroimino-hexahydro-triazines **11** using 2 equivalents of formaldehyde and 1 equivalent of *n*-propylamine.[9] Compounds **11** can be viewed as protected monosubstituted nitroguanidines thus allowing selective manipulations at the H-N(3) group. Treatment of **11** with methyl iodide in DMF in the presence of K_2CO_3 led to compounds **12a** and **12b** in yields of 62 and 60%, respectively.[10,11] ^{1}H NMR analysis of the crude material revealed that no other alkylation products were formed.

Alternatively, compounds **12** could be prepared from *N*-methyl-*N*′-nitroguanidine (**4**), which was obtained in 94% yield from *S*-methyl-*N*-nitroisothiourea (**10**) and methylamine,[8] via the nitroimino-hexahydro-triazine **13**.[9] The alkylation of **13** with heteroarylmethyl chlorides **14** proceeded with excellent yields,[10] making this route especially attractive.

To complete the synthesis of the target compounds **3**, we required a method to cleave the N–CH_2–N bonds in compounds **12**. After some experimentation,[12] it was found that treatment of **12** with 1N HCl at room temperature for 24 h afforded the *N*,*N*′-disubstituted-*N*″-nitroguanidines **3** in excellent yields.[13]

In conclusion, novel methodology has been developed for the preparation of *N*,*N*′-disubstituted-*N*″-nitroguanidines. This methodology was successfully applied to the synthesis of the neonicotinoids **3a** and **3b** from *S*-methyl-*N*-nitroisothiourea (**10**). Compounds **3a** and **3b** were obtained via alkylation of the nitroimino-hexahydro-triazine **13** with heteroarylmethyl chlorides

14 in overall yields of 63 and 66%, respectively. The alternative route, involving alkylation of the nitroimino-hexahydro-triazines **11** with methyl iodide, afforded **3a** and **3b** in overall yields of 39 and 38%, respectively.

References

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2. Kristiansen, O.; Maienfisch, P.; Gsell, L. European Patent Appl. EP 418199 A2 19910320 (1991); *Chem. Abst.* **1991**, *115*, 71586.
3. Independently of our work, two other research groups discovered the insecticidal properties of compounds **2** and filed patent applications a few months ahead of us. (a) Uneme, H.; Iwanaga, K.; Higuchi, N.; Minamida, I.; Okauchi, T. European Patent Appl. EP 376279 A2 19900704 (1990); *Chem. Abst.* **1991**, *114*, 61934. (b) Shiokawa, K.; Tsuboi, S.; Moriya, K.; Hattori, Y.; Honda, I.; Shibuya, K. European Patent Appl. EP 375907 A1 19900704 (1990); *Chem. Abst.* **1991**, *114*, 159163.
4. Uneme, H.; Iwanaga, K.; Higuchi, N.; Kando, Y.; Okauchi, T.; Akayama, A.; Minamida, I. *Pest. Sci.* **1999**, *55*, 202.
5. Preparation described in Scheme 2.
6. For additional examples, see: Maienfisch, P.; Kristiansen, O.; Gsell, L. European Patent Appl. EP 483062 A2 19920429 (1992); *Chem. Abst.* **1992**, *117*, 26353. An alternative method has recently been published.[4]
7. Fishbein, I.; Gallaghan, J. A. *J. Am. Chem. Soc.* **1954**, *76*, 1877.
8. General procedure for the synthesis of monosubstituted nitroguanidines **4** and **6**: A mixture of **10** (0.1 mol) and a primary amine (0.1 mol of **9** or 0.12 mol of an 8 M solution of methylamine in ethanol) in ethanol (100 ml) was heated to 80/50°C for 16 h. After being allowed to cool to room temperature, the products crystallised out of the reaction mixture. Filtration afforded the monosubstituted nitroguanidines **4** and **6** in pure form. Physical data for compounds **4**, **6a** and **6b**: compound **4**: m.p. 160–162°C; ^{1}H NMR (250 MHz, d_6-DMSO): 8.59 (bs, 1H), 7.85 (bs, 1H), 2.76 (bs, 3H); compound **6a**: m.p. 197–199°C; ^{1}H NMR (250 MHz, d_6-DMSO): 8.97 (bs, 1H), 8.38 (d, $J=2$ Hz, 1H), 8.08 (bs, 2H), 7.79 (dd, $J_1=7$ Hz, $J_2=2$ Hz, 1H), 7.55 (d, $J=7$ Hz, 1H), 4.44 (bd, $J=3$ Hz, 2H); compound **6b**: m.p. 167–169°C; ^{1}H NMR (250 MHz, d_6-DMSO): 8.0–9.8 (m, 1H), 8.09 (bs, 2H), 7.60 (s, 1H), 4.53 (bs, 2H).
9. General procedure for the synthesis of 1-substituted-2-nitroimino-hexahydro-1,3,5-triazines **11** and **13**: A mixture of the monosubstituted nitroguanidine (0.1 mol), *n*-propylamine (0.1 mol) and 15.2 ml of 37% aqueous formaldehyde solution (0.2 mol) in ethanol (50 ml) was heated to 50°C for 5 h. After being cooled to rt or 0°C, the products crystallised out of the reaction mixture. Filtration afforded the products in pure form. Physical data for compounds **11a**, **11b** and **13**: compound **11a**: m.p. 115–117°C; ^{1}H NMR (250 MHz, $CDCl_3$): 9.60 (bs, 1H), 8.32 (d, $J=2$ Hz, 1H), 7.80 (dd, $J_1=7$ Hz, $J_2=2$ Hz, 1H), 7.36 (d, $J=7$ Hz, 1H), 4.61 (s, 2H), 4.40 (bd, $J=2$ Hz, 2H), 4.28 (s, 2H), 2.50 (t, $J=7$ Hz, 2H), 1.37 (tq, $J_t=J_q=7$ Hz, 2H), 0.86 (t, $J=7$ Hz, 3H); compound **11b**: m.p. 127–128°C; ^{1}H NMR (250 MHz, d_6-DMSO): 9.35 (bs, 1H), 7.72 (s, 1H), 4.60 (s, 2H), 4.42 (s, 2H), 4.30 (bd, $J=2$ Hz, 2H), 2.30 (t, $J=7$ Hz, 2H), 1.33 (tq, $J_t=J_q=7$ Hz, 2H), 0.76 (t, $J=7$ Hz, 3H); compound **13**: m.p. 84–86°C; ^{1}H NMR (250 MHz, $CDCl_3$): 9.49 (bs, 1H), 4.38 (bd, $J=2$ Hz, 2H), 4.30 (s, 2H), 3.02 (s, 3H), 2.71 (t, $J=7$ Hz, 2H), 1.56 (tq, $J_t=J_q=7$ Hz, 2H), 0.97 (t, $J=7$ Hz, 3H).
10. General procedure for the alkylation of 1-substituted-2-nitroimino-hexahydro-1,3,5-triazines **11** and **13**: A mixture of the 1-substituted-2-nitroimino-hexahydro-1,3,5-triazine (0.075 mol), a heteroarylmethyl chloride **14** (0.075 mol) or methyl iodide (0.113 mol) and K_2CO_3 (25.8 g, 0.186 mol) in 150 ml of DMF was heated to 50°C (40°C; if methyl iodide is used as alkylation agent) for 16 to 20 h. After filtration and concentration, the crude product was recrystallised from methanol or purified by chromatography on silica gel using CH_2Cl_2/MeOH 19:1 as eluent to afford compounds **12** in pure form. Physical data for compounds **12a** and **12b**: compound **12a**: m.p. 139–141°C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.32 (d, $J=2$ Hz, 1H), 7.79 (dd, $J_1=7$ Hz, $J_2=2$ Hz, 1H), 7.37 (d, $J=7$ Hz, 1H), 4.66 (s, 2H), 4.35 (s, 2H), 4.25 (s, 2H), 3.07 (s, 3H), 2.54 (t, $J=7$ Hz, 2H), 1.34 (tq, $J_t=J_q=7$ Hz, 2H), 0.83 (t, $J=7$ Hz, 3H); compound **12b**: m.p. 84–85°C; ^{1}H NMR (250 MHz, $CDCl_3$): 7.49 (s, 1H), 4.73 (s, 2H), 4.35 (s, 4H), 3.05 (s, 3H), 2.57 (t, $J=7$ Hz, 2H), 1.40 (tq, $J_t=J_q=7$ Hz, 2H), 0.88 (t, $J=7$ Hz, 3H).

11. Other reaction conditions gave less satisfactory results. For example, alkylation with NaH as base and DMF or CH_3CN as solvent afforded compounds **12** in much lower yields. This is probably due to the high base sensitivity of nitroimino-hexahydro-1,3,5-triazines.
12. Strong acids such as aqueous HCl gave better results than acetic acid.[6]
13. General procedure for the hydrolysis of 1,3,5-trisubstituted-2-nitroimino-hexahydro-1,3,5-triazines **12**: To a solution of **12** (0.015 mol) in EtOH (30 ml) was added 1N HCl (30 ml) and the resulting reaction mixture was stirred at room temperature for 24 h. After being cooled to 0°C, the products crystallised out of the reaction mixture. Filtration afforded products **3** in pure form. Physical data for compounds **3a** and **3b**: compound **3a**: m.p. 159–160°C; ^{1}H NMR (250 MHz, d_6-DMSO): 9.13 (bs, 1H), 8.37 (d, $J=2$ Hz, 1H), 7.88 (bs, 1H), 7.82 (dd, $J_1=7$ Hz, $J_2=2$ Hz, 1H), 7.51 (d, $J=7$ Hz, 1H), 4.44 (bd, $J=4$ Hz, 2H), 2.85 (bd, $J=3$ Hz, 3H); compound **3b**: m.p. 174–175°C; ^{1}H NMR (250 MHz, d_6-DMSO): 9.16 (bs, 1H), 7.98 (bs, 1H), 7.61 (s, 1H), 4.50 (bd, $J=5$ Hz, 2H), 2.82 (bd, $J=5$ Hz, 3H).