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# First Synthesis of 4-Substituted Benzenesulfonylcyanoguanidines

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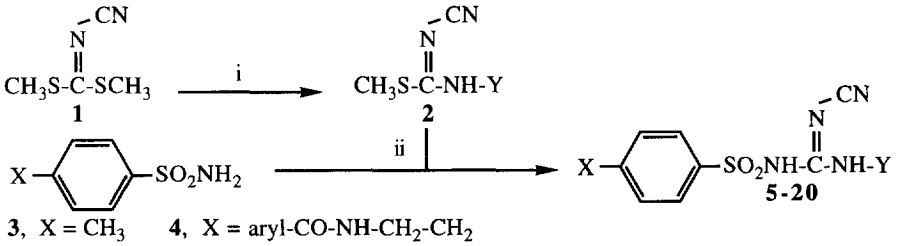
**Abstract:** N'-substituted-N-cyano-S-methylcarbamimidothioates react with 4-substitutedbenzene sulfonamides to give the corresponding sulfonylcyanoguanidines.



The cyanoguanidine group is regarded as a non-classical bioisostere of the urea and thiourea function[1]. This concept has been developed for the gastric antisecretory N'-alkyl-N-imidazolylalkylthioureas to give cimetidine[2]. Conversly, N'-alkyl-N-substituted pyridyl-thioureas and -ureas were found to be as active as pinacidil, an antihypertensive cyanoguanidine[3,4]. In the present study, we have applied this strategy to hypoglycemic sulfonylureas to obtain original drugs bearing a new moiety: the sulfonylcyanoguanidine function.



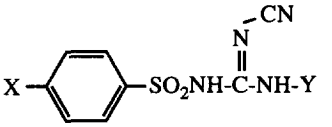

**Scheme 1** *Reagents :* i, Y-$NH_2$ (1.5 equiv), ethanol, 25°C; ii, NaOH (1 equiv), DMF, dioxane, reflux.

The N"[4-(substitutedphenyl)sulfonyl]-N'-substituted-N"cyanoguanidines **5-20** (table 1) were prepared by refluxing an excess (1.2 equiv) of N'-substituted-N-cyano-S-methylcarbamimidothioate **2** with the sodium salt of 4-methylbenzenesulfonamide **3**[5] or the 4-substitutedcarboxamidoethylbenzenesulfonamide **4**[6] (scheme 1). The carbamimidothioates **2** were synthesized by stirring a mixture of N-cyano-S,S'-dimethylimino carbonate **1**[7] in ethanol with the required amine (Y-$NH_2$, 1.5 equiv).

The compounds **7**, **8**, **12** and **13** are the bioisosteres of tolbutamide, tolcyclamide, tolazamide and gliclazide, the main representatives of the hypoglycemic drugs of first chemical generation (X = $CH_3$)[8]. The antidiabetic sulfonylureas bearing a substituted carboxamidoethyl side-chain belong to the second chemical generation. Compound **16** is the bioisostere of glibenclamide, one of the most potent hypoglycemic drug[8]. The electron-withdrawing groups ($SO_2$ and =N-CN) should maintain the acidity of the moiety as compared to the sulfonylurea function. The $^1$H-NMR spectra[9] of **7** (δ = 5.6, 2H, br s) and **16** (δ = 4.7, 2H, br s) revealed that both protons of the cyanoguanidine moiety were not distinguishable and located with the residual water contained in DMSO-$d_6$. On the contrary, tolbutamide (δ = 10.41, 1H, br s; 6.30, 1H, br t) and glibenclamide (δ = 10.27, 1H, br s; 6.25 1H, br d), their sulfonylurea counterparts, clearly exhibited three different signals corresponding to the two urea protons and residual water. These data suggest tautomeric forms of the sulfonylcyanoguanidine moiety and a higher lability of their acidic proton as compared to their sufonylurea bioisosteres. The chemical shift values lead to the proposal that **7** is probably more acidic than **16**, as it is

reported for tolbutamide (pKa = 5.3)[10] compared to glibenclamide (pKa = 6.8)[11]. All compounds were characterized by analytical and spectral methods[9].

**Table I :** Synthesis of 4-substitutedbenzenesulfonylcyanoguanidines



| N° | X | Y | Yield (%) | Mp (°C)[a] |
|---|---|---|---|---|
| **5** | $CH_3$ | $C_2H_5$ | 17 | 131-133 |
| **6** | $CH_3$ | $(CH_3)_2CH$ | 72 | 132-134 |
| **7** | $CH_3$ | $CH_3(CH_2)_3$ | 28 | 108-110 |
| **8** | $CH_3$ | cyclohexyl | 79 | 156-158 |
| **9** | $CH_3$ | cycloheptyl | 78 | 144-146 |
| **10** | $CH_3$ | (±)4-$CH_3$cyclohexyl | 52 | 163-165 |
| **11** | $CH_3$ | $(CH_2)_5N$ | 14 | 210-212 |
| **12** | $CH_3$ | $(CH_2)_6N$ | 22 | 193-195 |
| **13** | $CH_3$ | 1-azabicyclo[3,2,1]octane | 19 | 186-188 |
| **14** | $C_6H_5CONHCH_2CH_2$ | cyclohexyl | 76 | 174-176 |
| **15** | 4-$CH_3OC_6H_4CONHCH_2CH_2$ | cyclohexyl | 26 | 176-178 |
| **16** | 2-$CH_3$O,5-$ClC_6H_3CONHCH_2CH_2$ | cyclohexyl | 50 | 92-95 |
| **17** | 2-$CH_3$O,5-$ClC_6H_3CONHCH_2CH_2$ | (±)4-$CH_3$cyclohexyl | 64 | 85-87 |
| **18** | 2-furfurylCONHCH$_2$CH$_2$ | cyclohexyl | 55 | 146-148 |
| **19** | $C_6H_5NHCONHCH_2CH_2$ | cyclohexyl | 37 | 108-110 |
| **20** | 4-$ClC_6H_4NHCONHCH_2CH_2$ | cyclohexyl | 82 | 128-130 |

[a] All compounds were crystallized from ethanol.

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9 The elemental analyses for C,H,N,S are within 0.4% of the theorical values and were performed on a Carlo Erba 1108 analyzer. All new compounds gave IR and $^1$H-NMR spectra in accordance with their proposed structure. **7**: $^1$H-NMR (80 MHz, d$_6$-DMSO) δ 7.65 (2H, d, *J*=8Hz), 7.30 (2H, d, *J*=8Hz), 5.60 (2H, m), 3.15 (2H, br s), 2.30 (3H, s), 1.65-1.25 (4H, m), 0.8 (3H, t). IR (KBr) 2199 cm$^{-1}$ (C≡N st). **16**: $^1$H-NMR (80 MHz, d$_6$-DMSO) δ 8.18 (1H, m), 7.75 (2H, d), 7.58 (1H, d), 7.4 (3H, dd), 7.05 (1H, d), 4.70 (2H, br s), 3.72 (3H, s), 3.25-3.65 (3H, m), 2.95 (2H, m), 1.80-0.95 (10H, m). IR (KBr) 2188 cm$^{-1}$ (C≡N st).

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