Note

Nucleophilic substitutions on 3-chloro-4-fluoronitrobenzene

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Nucleophilic substitutions on 3-chloro-4-fluoronitrobenzene 5 with piperazines occur on the fluorine rather than on the chlorine atom as reported, to yield 3-chloro-4-piperazinylnitrobenzenes 8 and 9.

Our interest in antibacterial 6-fluoro-7-piperazinylnicotinolones like ciprofloxacin 1 and pefloxacin 2 led us to consider 4-fluoro-3-(substituted)-piperazinylnitrobenzenes 3 and 4 as starting materials in one route. A recently published Indian Patent 2 reported the formation of 3 in 90% yield from 3-chloro-4-fluoronitrobenzene 5 by reaction with N-acetyl piperazine 6 in pyridine at 120-125°C for 4 hr. The patent further describes the conversion of 3 into ciprofloxacin 1 via several obvious steps. A priori the substitution of chlorine meta to nitro group in 5 in preference to the intrinsically more reactive fluorine at position - 4 which is further activated by a para-placed nitro group seemed unlikely, but the patent claim had to be tested since 1 had been reportedly obtained from 3.

In the event, the reaction of 5 with 6 in pyridine at 120-125°C for 4 hr gave a yellow product. m.p. 91.92°C (from MeOH) in poor yield [lit. m.p. claimed for 3, 48-51°C]. The reaction of 5 and 6 went better when heated neat at 60°C for 2 hr to afford the same product in 53% yield. Physical data however established the identity of the product beyond doubt as 8, arising from 5 by displacement of fluorine as expected and not chlorine. Analysis. Found: C, 50.72; H, 4.94; N, 14.83; M+ 283, 285. Calcd for C12H14ClN3O3: C, 50.81; H, 4.97; N, 14.82%; M+, 283.72; 1H NMR (60 MHz, CDCl3): 8.27 (C2-H, d, =2.5Hz), 8.13 (C6-H, dd, J =8.2, 2.5 Hz), 7.03 (C5- H, d, J =8Hz), 3.73 (4H at C- 3' and C- 5', unresolved m), 3.20 (4H at C- 2' and C-6', unresolved m), 2.1-5 (COCH3, s).

Condensation of 5 with N-methyl piperazine 7 should have given 4 according to the patent which would lead to pefloxacin 2 by the reaction sequence outlined therein. However, the reaction of 5 and 7 in pyridine at 120-125°C for 4 hr gave only 9 in 59% yield [m.p. 94-95°C (from MeOH)] and not 4. Analysis. Found : C, 51.82; H, 5.65; N, 16.32; M+ 255, 257. Calcd for C11H13ClN3O2: C, 51.67; H, 5.52; N, 16.47%; M+ 255.71; 1H NMR (60 MHz, CDCl3): 8.18 (C2-H, d, J =2.5 Hz), 8.03 (C6-H, dd, J =8, 2.5 Hz), 7.03 (C5- H, d, J =8 Hz), 2.15 (COCH3, s).
C-6', m), 2.57 (4H at C-3' and C-5', m), 2.32 (CH₃, s).

The regrettable conclusion that 3 and 4 which could well serve as starting materials for 1 and 2 respectively cannot be obtained from 5 by nucleophilic substitution thus becomes inevitable. We wish to point out that the conventional synthesis of 1, 2 and similar compounds depends upon a preferential nucleophilic substitution of chlorine in 10 with piperazines in the final step but now the chlorine is activated by a para-placed carbonyl group while the fluorine does not enjoy such activation.

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References

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