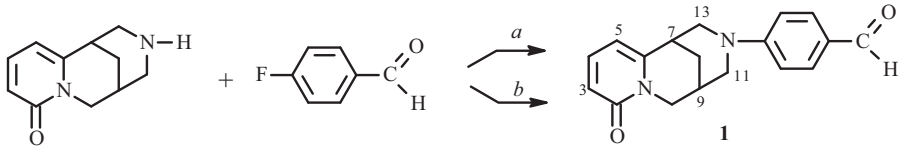
*Chemistry of Natural Compounds, Vol. 48, No. 3, July, 2012 [Russian original No. 3, May-June, 2012]*

# PREPARATION OF 4-(*N*-CYTISINYL)BENZALDEHYDE

**O. A. Nurkenov, S. D. Fazylov, A. E. Arinova, and I. V. Kulakov*** UDC 547.94

Methods for preparing amino-substituted aromatic benzaldehydes from the corresponding amines (morpholine, piperidine) and *o*-fluorobenzaldehydes in refluxing DMF in the presence of potash were reported [1]. The synthesized amino-substituted aromatic aldehydes were then used to synthesize important heterocyclic spiro-derivatives of quinolines. Because aldehydes are important sythons in the organic synthesis of various classes of compounds, including heterocyclic ones, we attempted to prepare an aromatic aldehyde with a biologically active fragment, in particular, the alkaloid cytisine.

In analogy with the reported procedure [1], we substituted the F atom in 4-fluorobenzaldehyde by the alkaloid cytisine.




**1**

*a*. $K_2CO_3$, DMF, 150°C, 20–25 h; *b*. $SiO_2 \cdot K_2CO_3$, DMF, MW, 30 min

The performance of this reaction was complicated by its length (>20 h) although the yield of **1** was satisfactory (40–45%).

Microwave (MW) activation is known to decrease significantly the reaction time from several hours or days to several minutes. The reaction rate increases by tens and hundreds of times. Use of MW radiation can also enable many syntheses that could not be carried out under standard classical conditions to be performed. The selectivity and direction of the reactions can also change [2, 3]. A unique procedural feature of synthesis using MW radiation is the use of a solid support, i.e., a material that is transparent in the ultra-high-frequency range but exhibits catalytic properties on the surface of which the fundamental reaction steps occur [4–6].

We studied the preparation of **1** using MW activation in order to increase the yield. The preparation of **1** could be carried out successfully in 30 min in DMF using MW radiation with a silica-gel support.

We used a specially prepared catalyst on silica-gel support (Silpearl) activated by double the amount of potash for the reaction. The potash was dissolved in a small amount of $H_2O$ into which the silica gel was suspended in order to distribute the potash evenly on the silica gel. The water was evaporated. The resulting dry solid was thoroughly ground in a mortar and dried at 120°C.

The PMR spectrum of **1** showed resonances for the cytisine protons at practically the characteristic regions with the exception of H-11 and H-13, which were found at weaker field because of the shielding effect of the adjacent aromatic ring. Even the H-8 methylene protons, in contrast with previously described cytisine derivatives [7–9], appeared not as two characteristic doublets but as a broad triplet. The H-5 aromatic proton of the dihydropyridine ring experienced a weak-field shift relative to the H-3 proton that was uncharacteristic of all described cytisine derivatives. This could be explained by possible shielding related to the formation of a H-bond between H-5 and the carbonyl on the phenyl ring that was probably situated in space parallel to the plane of the dihydropyridine ring, analogously to a structure reported by us earlier [7]. The aldehyde proton appeared as a narrow singlet at 9.66 ppm.

The synthesized derivative **1** could represent an exceedingly promising synthon for incorporating biologically active cytisine into various derivatives.

PMR spectra were recorded in DMSO-$d_6$ with TMS internal standard on a Bruker DRX500 spectrometer at operating frequency 500 MHz. IR spectra were taken in KBr pellets on an Avatar-320 Fourier-transform spectrometer. Mass spectra

Institute of Organic Synthesis and Carbon Chemistry of the Republic of Kazakhstan, Kazakhstan, 100008, Karaganda, Ul. Alikhanova, 1, fax: (87212) 41 38 66, e-mail: kulakov_iv@mail.ru. Translated from *Khimiya Prirodnykh Soedinenii*, No. 3, May–June, 2012, pp. 472–473. Original article submitted November 13, 2011.

0009-3130/12/4803-0527  

were measured in a Finnigan MAT.INCOS 50 instrument by direct sample introduction at ionizing energy 70 eV. Melting points were determined on a Boetius apparatus. TLC was performed on Sorbfil plates with detection by $I_2$.

**4-(*N*-Cytisinyl)benzaldehyde (1). Synthesis Under Classical Conditions.** A solution of 4-fluorobenzaldehyde (1.50 g, 0.02 mol) in DMF (25 mL) was treated with cytisine (2.32 g, 0.022 mol) and potash (2.76 g, 0.04 mol) and refluxed at 140–150°C for 25 h. The excess of DMF was distilled off. The residue was diluted in $H_2O$ (100 mL). The product was extracted with EtOAc (3 × 60 mL). The combined extracts were dried over anhydrous $Na_2SO_4$ and evaporated to dryness. The resulting solid was recrystallized from *i*-PrOH to afford **1** as transparent yellowish crystals (2.46g, 42%), mp 244–245°C (*i*-PrOH).

**Synthesis of 1 Using MW Radiation.** A solution of 4-fluorobenzaldehyde (1.50 g, 0.02 mol) in DMF (15 mL) was treated with cytisine (2.32 g, 0.022 mol) and supported catalyst (3.46 g). The mixture was irradiated with microwaves (in a commercial LG microwave oven) at 500 W power for 30 min with breaks (15 × 2 min). The mixture was worked up as above to afford transparent yellowish crystals (3.93 g, 67%), mp 244–245°C (*i*-PrOH). Elemental analysis of **1** agreed with the calculated values, $C_{18}H_{18}N_2O_2$. IR spectrum (KBr, ν, $cm^{-1}$): 1674 (C=O), 1655 (C=O). Mass spectrum (EI, 70 eV, *m*/*z*, $I_{rel}$, %): 294 (68) $[M]^+$, 149 (37), 148 (100), 146 (35), 132 (50), 118 (31), 91 (33), 77 (42). PMR spectrum (δ, ppm, J/Hz): 1.96 (2H, br.t, $J_{8,7} = J_{8,9} = 2.9$, H-8), 2.57 (1H, br.s, H-9), 3.085 (1H, br.d, J = 12.51, H-7), 3.154 (1H, dd, $J_{11a,11e} = 12.35$, $J_{11a,9} = 2.2$, H-11a), 3.25 (1H, br.d, $J_{13a,7} = 2.33$, H-13a), 3.725 (1H, dd, $J_{10a,9} = 5.94$, $J_{10a,10e} = 15.56$, H-10a), 3.94 (1H, d, $J_{10e,10a} = 15.47$, H-10e), 3.95 (1H, br.s, H-13e), 4.14 (1H, br.d, $J_{11e,11a} = 12.51$, H-11e), 6.15 (1H, dd, $J_{3,4} = 9.0$, $J_{3,5} = 1.3$, H-3), 6.22 (1H, dd, $J_{5,4} = 6.9$, $J_{5,3} = 1.3$, H-5), 6.91 (2H-Ar, d, J = 8.96), 7.32 (1H, dd, $J_{4,5} = 6.9$, $J_{4,3} = 9.0$, H-4), 7.62 (2H-Ar, d, J = 8.93), 9.66 [1H, s, C(O)H].

## REFERENCES


1. E. V. D′yachenko, T. V. Glukhareva, E. F. Nikolaenko, A. V. Tkachev, and Yu. Yu. Morzherin, *Izv. Akad. Nauk, Ser. Khim.*, 1191 (2004).
2. D. Villemin, B. Martin, and N. Bar, *Molecules*, **3**, 88 (1998).
3. M. Lacova, R. Gasparova, D. Loos, T. Liptay, and N. Pronayova, *Molecules*, **5**, 167 (2000).
4. Y. Wan, *J. Med. Chem.*, **47**, 5995 (2004).
5. M. Erdelyi and A. Gogoll, *Synthesis*, **11**, 1592 (2002).
6. J. K. Murray, *J. Am. Chem. Soc.*, **127**, 13271 (2005).
7. I. V. Kulakov, D. M. Turdybekov, Z. M. Zhambekov, O. A. Nurkenov, B. T. Ibragimov, S. A. Talipov, and K. M. Turdybekov, *Khim. Prir. Soedin.*, 572 (2009).
8. I. V. Kulakov, O. A. Nurkenov, D. M. Turdybekov, and K. M. Turdybekov, *Khim. Prir. Soedin.*, 216 (2010).
9. I. V. Kulakov and D. M. Turdybekov, *Khim. Geterotsikl. Soedin.*, **46**, 1039 (2010).