Chemistry of Heterocyclic Compounds, Vol. 39, No. 6, 2003

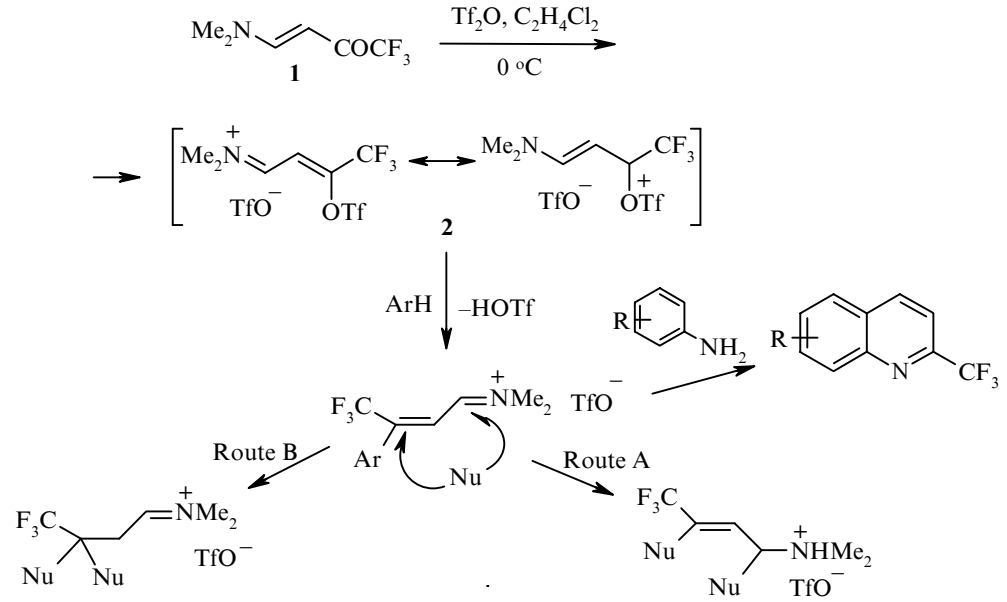
SYNTHESIS OF CF_3-HETEROCYCLES BASED ON 4-DIMETHYLAMINO-1,1,1-TRIFLUORO-3-BUTEN-2-ONE

I. L. Baraznenok, V. G. Nenajdenko, and E. S. Balenkova

Novel heterocyclizations have been investigated based on the reaction of the complex between trifluoromethanesulfonic anhydride and 4-dimethylamino-1,1,1-trifluoro-3-buten-2-one with 2,2'-biindolyl and N,N'-dipyrrolylmethane leading to closure of 6- or 7-membered rings.

Keywords: 2,2'-biindolyl, CF_3-heterocycles, iminium salt, trifluoromethanesulfonic anhydride.

We have previously [1, 2] reported a novel electrophilic reagent which is formed as a complex between 4-dimethylamino-1,1,1-trifluoro-3-buten-2-one (**1**) and trifluoromethanesulfonic anhydride and studied its behavior in reactions with a series of aromatic and heterocyclic substrates which contain electron-donor substituents. The complex (**2**) is a bifunctional electrophile being an iminium salt with a positive charge delocalized between the nitrogen atom, the carbonyl, and terminal olefine carbon atoms [1]. Its interaction with arenes and hetarenes is a variant of a vinylogous Vilsmeier–Haack reaction leading to the formation of trifluoromethyl-substituted cinnamaldehydes. The reaction of the given complex with anilines opens up a novel route to the synthesis of 2-trifluoromethyl-substituted quinolines [2].

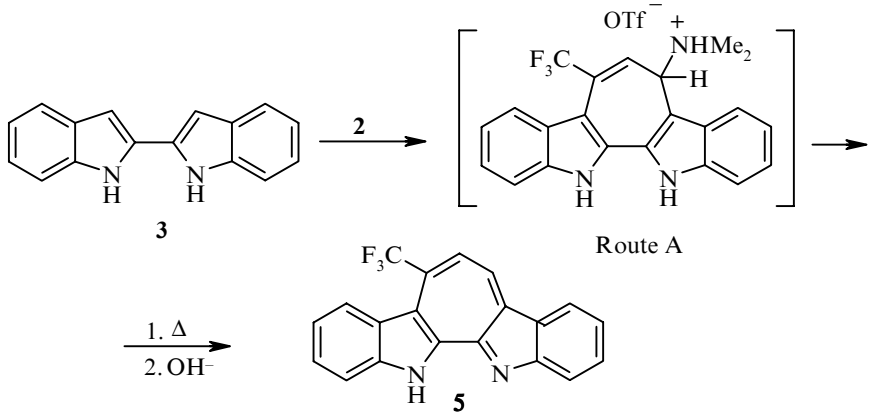


M. V. Lomonosov State University, Moscow 119899, Russia; e-mail: Nen@acylium.chem.msu.ru.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 904-907, June, 2003. Original article submitted June 19, 2000.

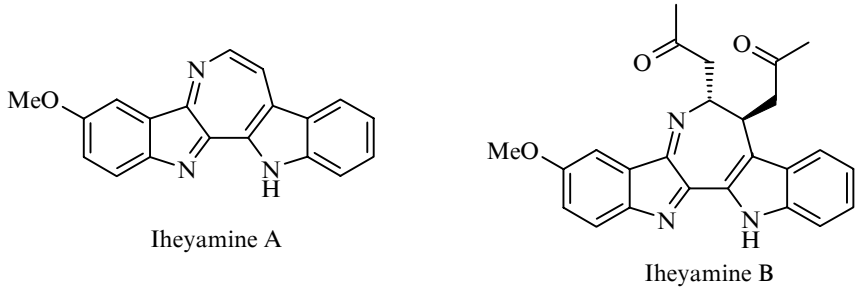
 0009-3122/03/3906-0776$25.00

Continuing a study of the synthetic potential of this reagent we have proposed that, for aromatic substrates of appropriate structure, cyclic compounds can be formed as has been observed previously in the case of 2-CF_3-quinolines. Moreover, thanks to the presence of two different electrophilic centers, various reaction routes are possible with electron-rich aromatic compounds with subsequent cyclization (route A and route B).

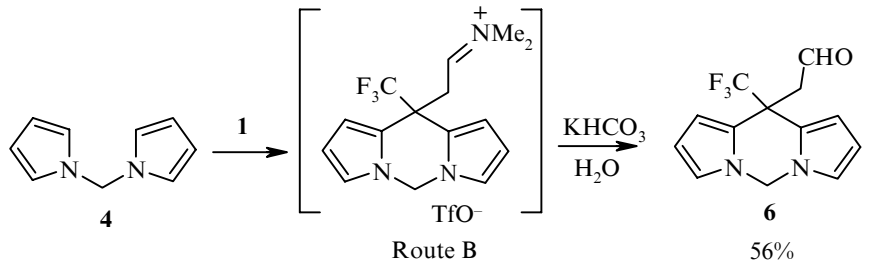
In order to study these cyclizations we have prepared the model substrates 2,2'-biindolyl (**3**) [3] and N,N'-dipyrrolylmethane (**4**) [4]. It was found that the reaction of the iminium complex with 2,2'-biindolyl gave a single, amorphous reaction product which had an intense, dark-red coloration and very low solubility in all of the solvents studied by us. Based on combined NMR, IR, and elemental analytical data we found that the obtained compound **5** is the product of cyclization at the most active positions (3 and 3') of the indole nuclei. Hence, the formation of a seven membered ring occurs, moreover the substance has a fully aromatic structure (an azaazulene derivative) and signals for the protons and carbons of an aliphatic residue are absent in their NMR spectra.



Alkaloids with this carbon skeleton occur in nature in the iheyamines A and B [5] which have been separated from *Polycitorella sp.* and they were found to possess high cytotoxicity



A quite different reaction occurs with the dipyrrolylmethane **4**. The single reaction product isolated in moderate yield is the aldehyde **6** which is the cyclization product *via* route B.



It should be noted that such a reaction course for this reagent had been observed by us previously for the first time as evident in the attack of nucleophiles either occurring at the vinyltriflate center or involving two different reaction centers (vinyltriflate and iminium) in the reagent. Evidently, in this case, such a reaction course is associated with the preferred formation of a six membered ring and low probability of closure to an eight membered ring.

Hence we have synthesized novel trifluoromethyl-substituted heterocyclic derivatives based on 4-dimethylamino-1,1,1-trifluoro-3-buten-2-one and have shown that cyclization can occur either at one or at two different centers of the reagent depending on the structure of the substrate.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz respectively) using $CDCl_3$ solvent and TMS internal standard. IR spectra were obtained on a UR-20 spectrometer using vaseline oil. TLC was carried out on Silufol UV-254 plates and revealed using acidified $KMnO_4$ solution or iodine vapor. Trifluoromethanesulfonic anhydride was prepared as in method [6].

2,2'-Biindolyl (3) was prepared from N,N'-bis(*o*-tolyl)oxamide using method [3] and purified by recrystallization from a mixture of dioxane and acetic anhydride (5:3). Yield 64%; mp 258°C (decomp.), lit. mp 260°C (decomp.) [4].

N,N'-Dipyrrolylmethane (4) was prepared by method [4] and purified by recrystallization from hexane. Yield 44%; bp 150°C, mp 37-38°C, n_D^{20} 1.4780. According to data in [5], bp 151°C, n_D^{20} 1.4790.

7-Trifluoromethyl-12H-indolo[3',2':6,7]cyclohepta[1,2-*b*]indole (5). A solution of $(CF_3SO_2)_2O$ (0.82 g, 2.9 mmol) in absolute dichloroethane (5 ml) was added dropwise to a solution of enaminone **1** (0.48 g, 2.9 mmol) in absolute dichloroethane (10 ml) at 0°C with vigorous stirring and then 2,2'-biindolyl (0.67 g, 2.9 mmol) in absolute dichloroethane (15 ml) was added. The reaction mixture was stirred at room temperature for 4 h, poured into a mixture of ether and aqueous K_2CO_3 solution, the organic phase separated, and the aqueous layer extracted with ether and dried over Na_2SO_4. Solvent was evaporated in vacuo and the residue was recrystallized from chloroform to give 0.84 g (86%); mp 254-256°C (decomp.). IR spectrum, ν, cm^{-1}: 2850 (NH), 1610 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.84 (1H, d, *J* = 10.1, 6-H); 8.62 (1H, d, *J* = 7.8, 8-H); 8.34 (1H, d, *J* = 7.8, 4-H); 8.08 (1H, d, *J* = 10.1, 5-H); 7.70 (1H, d, *J* = 7.8, 1-H or 11-H); 7.65-7.61 (2H, m); 7.47 (1H, t, *J* = 7.8); 7.49 (1H, t, *J* = 7.6); 7.45 (1H, t, *J* = 7.7). ^{13}C NMR spectrum, δ, ppm (J, Hz): 148.40, 146.83, 145.80, 144.62, 133.35, 126.73, 125.50, 123.79 (8C, quat. arom); 131.55 (1C, q, *J* = 29.0, $C_{(7)}$); 129.72, 129.02, 128.84, 122.56, 122.34, 120.82, 116.63, 115.31 (8 CH_{arom}); 125.39 (1C, q, *J* = 8.0); 125.21 (1C, q, *J* = 277.3, CF_3); 117.50 (1C, q, *J* = 7.9). Found, %: C 70.98; H 3.21. $C_{20}H_{11}F_3N_2$. Calculated, %: C 71.43; H 3.30.

2-(10-Trifluoromethyl-10H-dipyrrolo[1,2-*c*:2,1-*f*]pyrimidin-10-yl)acetaldehyde (6). A solution of $(CF_3SO_2)_2O$ (0.82 g, 2.9 mmol) in absolute dichloroethane (5 ml) was added dropwise to a solution of the enaminone **1** (0.48 g, 2.9 mmol) in absolute dichloroethane (10 ml) at 0°C with vigorous stirring and then N,N'-dipyrrolylmethane (0.42 g, 2.9 mmol) in absolute dichloroethane (15 ml) was added. The reaction mixture was stirred for 2 h at 30-35°C, poured into a mixture of ether and aqueous K_2CO_3 solution, the organic phase separated, and the aqueous layer extracted with ether and dried over Na_2SO_4. Solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column using hexane–ethyl acetate as eluent (10:1). Yield 55%; mp 122-124°C. IR spectrum, ν, cm^{-1}: 1730 (C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 9.01 (1H, t, *J* = 2.0, CHO); 6.83 (2H, m, 3'-, 7'-CH); 6.30 (4H, m, 1'-, 2'-, 8'-, 9'-CH); 5.97 (1H, d, *J* = 10.2, 5'-C<u>H</u>H); 5.90 (1H, d, *J* = 10.2, 5'-C<u>H</u>H); 3.26 (2H, d, *J* = 2.0, 2-CH_2). ^{13}C NMR spectrum, δ, ppm (*J*, Hz); 198.34 (C=O); 125.05 (q, CF_3, *J* = 280.7); 121.89 (2C, $C_{(9a)}$, $C_{(10a)}$); 119.50 (2 C); 109.84 (2 C); 109.13 (2 C); 58.88 ($C_{(5')}$); 44.36 ($C_{(2)}$); 141.2 (q, *J* = 29.7, $C_{(3)}$). Found, %: C 57.95; H 4.05. $C_{13}H_{11}F_3N_2O$. Calculated, %: C 58.21; H 4.13.

The work in this publication was carried with the partial support of the Russian Fund for Fundamental Research (grants Nos. 00-03-32763a and 00-03-32760a).

REFERENCES

1. I. L. Baraznenok, V. G. Nenaidenko (Nenajdenko), and E. S. Balenkova, *Tetrahedron*, **54**, 119 (1998).
2. I. L. Baraznenok, V. G. Nenaidenko (Nenajdenko), and E. S. Balenkova, *Eur. J. Org. Chem.*, 937 (1999).
3. J. Bergman, E. Koch, and B. Pelcman, *Tetrahedron*, **51**, 5631 (1995).
4. U. Burger and F. Dreier, *Helv. Chim. Acta*, **63**, 1190 (1980).
5. T. Sasaki, I. Ohtani, J. Tanaka, and T. Higa, *Tetrahedron Lett.*, **40**, 303 (1999).
6. P. J. Stang, M. Hanack, and L. R. Subramanian, *Synthesis*, No. 2, 85 (1982).