1,3-DIPOLAR CYCLOADDITION REACTION OF TRIFLUOROACETONITRILE WITH HETEROCYCLIC YLIDES.[1]

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Abstract: Trifluoroacetonitrile is found to be a good dipolarophile and reacts with heterocyclic N-ylides to give (trifluoromethyl)imidazolopyridine compounds.

Many trifluoromethylated compounds have been synthesized and used in various fields. However, the procedure for preparing these compounds are not usually easy. Now, we tried to synthesized condensed heterocyclic systems with a trifluoromethyl group by the 1,3-dipolar reaction of trifluoroacetonitrile in one step reaction. Trifluoroacetonitrile was reported to react as a dienophile with butadiene to give 2-(trifluoromethyl)pyridine.[2] We examined, 1,3-dipolar reaction of this nitrile[3] with heterocyclic ylides.

Treatment of 2-(ethoxycarbonylmethyl)isoquinolinium bromide (1) with trifluoroacetonitrile in the presence of triethylamine in methylene chloride gave 3-ethoxycarbonyl-2-(trifluoromethyl)imidazolo[2,1-a]isoquinoline (2) in 62% yield. 2: mp 154-6°C; ^{1}H-nmr δ (CDCl$_3$) 1.43 (3H, t, J=7.0 Hz), 4.45 (2H, q, J=7.0 Hz), 7.20 (1H, d, J=7.4 Hz), 7.7-7.8 (3H, bs), 8.60 (1H, m) and 8.95 (1H, d, J=7.4 Hz); ^{19}F-nmr δ^{4} -3.0; M/e 308 (M$^+$). Compound (2) seemed to be formed by oxidation of a primary adduct in work-up. Similar reaction of 2-phenacylisoquinolinium bromide (3) with trifluoroacetonitrile gave 3-benzoyl-2-(trifluoromethyl)imidazolo[2,1-a]-isoquinoline (4) and its 5,6-dihydro compound (5) in 4% and 5.2% yields. 4: mp 150-2°C; ^{1}H-nmr δ (CDCl$_3$) 7.20 (1H, d, J=8.0 Hz), 7.4-7.7 (6H, m), 7.82 (2H, d, J=8.0 Hz), 8.37 (1H, d, J=8.0 Hz) and 8.76 (1H, m); ^{19}F-nmr δ -2.0 (s); M/e 340. 5: mp 112-3°C; ^{1}H-nmr 3.17 (2H, t, J=7.0 Hz), 4.21 (2H, t, J=7.2 Hz), 7.2-7.7 (6H,m), 7.85 (2H, d, 8.0 Hz), and 8.12 (1H, m); ^{19}F-nmr δ -3.0 (s); M/e 342 (M$^+$). This result suggests that 2 and 4 were formed through dihydro compounds like 5 by the rearrangement and oxidation (Chart 1). 2-(Cyanomethyl)isoquinolinium chloride (6) gave 3-cyano analogue (7) of 2 in 20% yield. 7: mp 186-8°C; ^{1}H-nmr δ (CDCl$_3$)

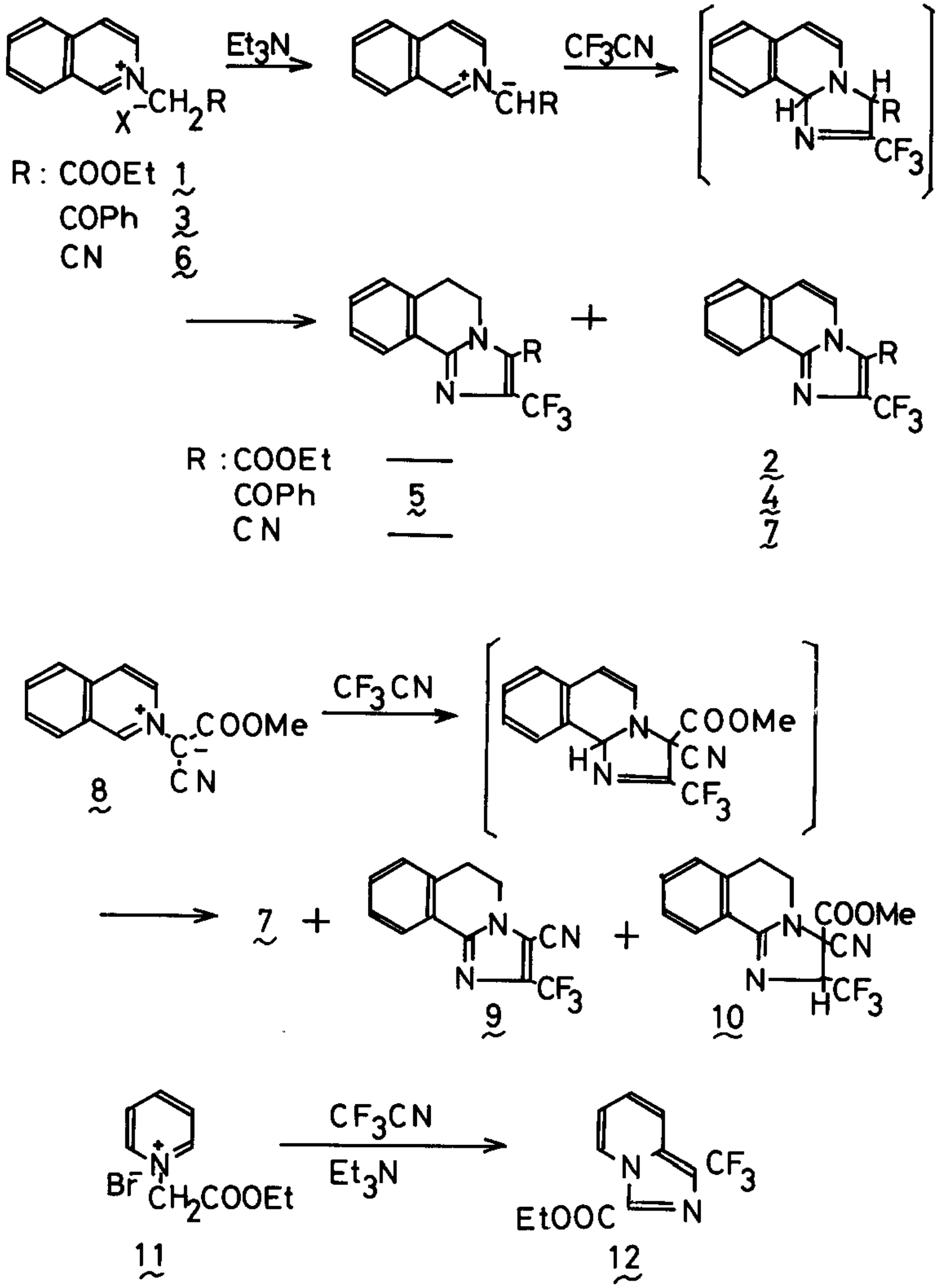
Et3N
CF3CN
X⁻
CH2R
CHR
H
R
CF3
R : COOEt 1
COPh 3
CN 6
R : COOEt —— 2
COPh 5 4
CN —— 7
8
COOMe
CN
9
10
7
11
Br⁻
CH2COOEt
12
EtOOC
N

Chart 1

7.43 (1H, d, J=7.6 Hz), 7.60-7.90 (3H, m), 8.07 (1H, d, J=7.6 Hz) and 8.67 (1H, m); ^{19}F-nmr δ -2.5 (s); M/e 261 (M^+). In these reactions, the yields were not optimized. The low yields in the latter two reactions may be due to the redox reactions of the primary adducts and further attack of excess trifluoroacetonitrile to these intermediates.

Very low yields of three products were isolated from the reaction of isoquinolinium cyano(methoxycarbonyl)methylide (**8**) with trifluoroacetonitrile. Thus, the compound (**7**) (2%), its 5,6-dihydro compound (**9**) (2%) and 3-cyano-3-methoxycarbonyl-2-trifluoromethyl-2,3,5,6-tetrahydroimidazolo[2,1-a]isoquinoline (**10**) (1%) were obtained. **9**: mp 213°C; ^{1}H-nmr δ ($CDCl_3$) 4.27 (2H, t, J=7.0 Hz), 5.36 (2H, t, J=7.0 Hz), and 7.4 (4H, b); ^{19}F-nmr δ -1.0 (s); M/e 263 (M^+). **10**: mp 95-97°C; ^{1}H-nmr δ 3.21 (2H, m), 3.90 (3H, s), 4.17 (2H, m), 5.23 (1H, m) and 7.18 (4H, m); ^{19}F-nmr δ -1.0 (d); M/e 323 (M^+). In this case, the presence of two substituent on the ylide carbon hindered the isomerization of the primary adduct and its much more complex reaction seemed to lower the yields of the products.

Ethoxycarbonylmethylpyridinium bromide (**11**) reacted in a similar way to **1** to give a imidazolopyridine compound (**12**) in 18% yield. **12**: mp 102-3°C; ^{1}H-nmr δ ($CDCl_3$) 1.42 (3H, t, J=7.2 Hz), 4.48 (2H, q, 7.2 Hz), 7.17-7.97 (3H, m), 9.40 (1H, d, J=6.2 Hz); ^{19}F-nmr δ -1.0 (s); M/e 258 (M^+). Other pyridinium methylides gave a very complex mixture of products, probably due to less stability of the products than those from isoquinolinium ylides. All results are summarized in Chart 1 with proposed mechanisms.

The above results show that trifluoroacetonitrile reacts as an active dipolarophile and is very useful for one-step syntheses of some trifluoromethyl compounds, which are otherwise very difficult to obtain.

References and Notes

1) Part of this work was reported at the 99th Annual Meeting of Pharmaceutical Society of Japan, 1979, Okayama.

2) J. M. S. Jarvice, W. E. Fitzgerald, and G. J. Janz, J. Am.Chem. Soc., 1956, **78**, 978.

3) CF_3CN is prepared by dehydration of CF_3CONH_2 with P_2O_5. This nitrile is a highly toxic gas and strict care should be taken for its use.

4) Up-field to internal $PhCF_3$.

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