CYCLOADDITION REACTIONS OF 6-CYANOBENZ[a]INDOLIZINES WITH ACTIVATED ALKYNES. FORMATION OF BENZO[2.2.3]- and [2.3.4]CYCLOAZINES

Kiyoshi Matsumoto*a, Takane Uchida*b, Tomoe Kato*b, Mitsuo Toda*a, Kinuyo Aoyama*b, and Hideyuki Konishi*c

a College of Liberal Arts and Science, Kyoto University, Kyoto 606, Japan
b Faculty of Education, Fukui University, Fukui 910, Japan
c Department of Chemistry, Aichi University of Education, Kariya 448, Japan

Abstract—Cycloaddition reactions of 6-cyanobenz[a]indolizines with activated alkynes such as dimethyl acetylenedicarboxylate, diacetylenecarboxylic anhydride, methyl propiolate, methyl trimethylsilylpropiolate, methyl phenylpropiolate, and 4-phenyl-3-butyn-2-one were investigated.

Previously, we have described in full detail preparation of 6-cyanobenz[a]indolizines which are activated by means of aromatic stabilization in favor of the azomethine ylide structure. Indeed, they readily undergo [8+2] cycloaddition with dibenzoylethylene giving the 1,2-dibenzoylindolizin[3,4,5-ab]isoindoles. In contrast, 3-cyanoindolizines only sluggishly reacted even with dimethyl acetylenedicarboxylate to afford the corresponding [2.2.3]cyclazines and/or a novel type of the 1:2 molar products. We now report further examples of cycloaddition reactions of 6-cyanobenz[a]indolizines with electron deficient alkynes.

Reaction of 6-cyanobenz[a]indolizine (1a) with excess dimethyl acetylenedicarboxylate (DMAD) in refluxing toluene in the presence of Pd-C for 2 h gave (2a) (13%) along with the 1:1 adduct 3a (7%). Di-t-butyl acetylenedicarboxylate (DBAD) is potentially an acetylene equivalent since at high temperature of ca. 270°C t-butoxycarbonyl group was converted to hydrogen with extrusion of carbon dioxide and isobutylene. Unfortunately, however, DBAD has often proved to serve as an acetylenedicarboxylic anhydride (C₄O₃) rather than an acetylene
\[ R_1 = fC\text{H}=\text{CH}f_2 = R_2 \]
\[ 1a: R_1 = R_2 = \text{H} \]
\[ b: R_1 = \text{H}, R_2 = \text{Me} \]
\[ c: R_1 = \{\text{CH}=\text{CH}\}_2 = R_2 \]
\[ 2a: X = Y = \text{CO}_2\text{Me} \]
\[ b: X = Y = \text{H} \]
\[ c: X = Y = \text{CO}_2\text{Bu-t} \]
\[ d: X = Y = \text{COMe} \]
\[ e: X = \text{CO}_2\text{Me}, Y = \text{H} \]
\[ f: X = \text{H}, Y = \text{CO}_2\text{Me} \]
\[ g: X = \text{CO}_2\text{Me}, Y = \text{SiMe}_3 \]
\[ h: X = \text{SiMe}_3, Y = \text{CO}_2\text{Me} \]
\[ i: X = \text{CO}_2\text{Me}, Y = \text{Ph} \]
\[ j: X = \text{Ph}, Y = \text{CO}_2\text{Me} \]
\[ k: X, Y = \text{Ph}, \text{COMe} \]

\[ \sim a: X = Y = \text{CO}_2\text{Me} \]
\[ c: X = Y = \text{CO}_2\text{Bu-t} \]

\[ \overset{1c}{\text{2 DMAD}} \]
\[ \overset{1,5-\text{Dipolar}}{\text{& Diels-Alder}} \]
\[ \overset{\text{Cycloaddition}}{\text{rearrangement}} \]
\[ (E = \text{CO}_2\text{Me}) \]

\[ \overset{5}{\sim} \]

\[ \overset{4}{\sim} \]
equivalent.6 Thus, it is interesting to note that at 210°C in nitrobenzene for 4 h 1 with excess DBAD produced indolizin[3,4,5-ab]isoindole (2b) in 9% yield, whereas at about 100°C for 21 h in toluene gave a mixture of 2c (14%) and the 1:1 adduct 3c (42%). Curiously enough, isoindolo[1,2-ab]isoquinoline (1c) with DMAD gave the 1:2 molar adduct in 41% yield. The structure was tentatively assigned as 47 that could be derived from the same type of an intermediate "proposed" in the novel formation of the pyrroles from 3-cyanoindolizines and DMAD.3 Intriguingly, diacetylacetylene with 9-methyl-6-cyanobenz[a]indolizine (1b) gave the [2.3.4]cyclazine 5 albeit in 7% yield, while 1a afforded the benzol[2.2.3]cyclazine 2d in 8% yield.

As a matter of course, reactions of 1 with several unsymmetric alkynes were also examined. Trimethylsilylacetylene and phenylacetylene were inert to 1a in refluxing toluene and xylene. 1a with excess methyl propiolate in refluxing toluene for 34 h gave the benzol[2.2.3]cyclazine as a single product. Its regiochemistry was tentatively assigned as 2e by an inspection of the mass fragmentation patterns of 2e and the related [2.2.3]cyclazines.8 Methyl trimethylsilylpropiolate with 1a under similar conditions (72 h) afforded a mixture of 2e7 (5%), 2f (5%), 2g (11%), and 2h (14%).8 An analogous reaction (45 h) of methyl phenylpropiolate with 1a gave the corresponding cyclazines 2l and 2j in 52 and 6% yields respectively, their regiochemical assignments being based on the mass spectral fragmentation pattern.8,9 Such desilylation during cycloaddition reactions is not unprecedented.10 4-Phenyl-3-butyn-2-one, likewise(72 h), underwent cycloaddition onto 1a yielding a mixture of the regioisomers 2k (48 and 7%). In this case, the regiochemical assignment could not be made.

ACKNOWLEDGMENT

This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture (Nos. 61840017, 62540377, and 62430007).

REFERENCES

3. K. Matsumoto, C. Kabuto, T. Uchida, H. Yoshida, T. Ogata, and M. Iwaizumi,
4. All the new compounds described in this paper had satisfactory elemental and/or exact mass analyses along with $^1$H- and $^{13}$C-NMR and IR spectra. Data of mp(°C): 2a, 190; 2b, 76-78; 2c, 125; 2d, 123-125; 2e, 42-48; 2f, 74-78; 2g, 118-120; 2h, 157-159; 2i, 137-139; 2j, 133-134; 2k, 94-96 and 118-120; 3a, 139-142; 3c, 148; 4, 179-180; 5, 187-189.


7. An X-ray analysis of this compound is envisaged.

8. Representative examples of mass spectral fragmentation patterns are followings:

9. Preliminary frontier orbital considerations based upon HMO calculations are in accord with such assignments. More sophisticated MO calculations like CNDO/2 are in progress.


Received, 23rd January, 1990