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LETTERS

Methyl 4,6-Dichloro-3-diethylaminofuro[3,4-*c*]pyridine-1-carboxylate: Synthesis of the First Stable Azaisobenzofuran by a Hamaguchi-Ibata Reaction

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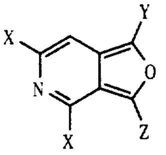
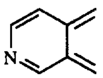
In memory of P. C. Dutta

***Abstract*:** The title compound, an intermediate in the Hamaguchi-Ibata reaction involving the Rh^{II}-catalysed intramolecular reaction of a diazo group with the carbonyl of an adjacent amido group has been isolated and characterized. PM3 calculations reveal the heat of formation(ΔH_f) of this remarkably stable molecule to be −77.69 kcal/mol.

Although a great deal of theoretical, structural and reactivity studies have provided a rich understanding of the chemistry of isobenzofurans,[1] little, if any, work has been done with the analogous furo[*c*]pyridines.[2] The parent furo[3,4-*c*]pyridine **1** was reported as early as 1977 as a white crystalline solid, stable only at low temperature, but undergoing rapid polymerization at about room temperature.[3] More recently, the 1,3-dimethyl derivative of **1**, *viz*., **2** was also made and was found stable enough to be characterized by ^{1}H-NMR spectroscopy.[4] Although not isolated, substituted isobenzofurans[1] and azaisobenzofuran **3**[5] have been implicated as reactive intermediates in the synthesis of polyaromatic ring systems by tandem Hamaguchi-Ibata[6,7] and Diels-Alder reactions. A recent resurgence[8] of interest in labile pyridine *o*-quinodimethanes *e.g*., **7** and the appearance of a report[9] on the Diels-Alder reaction of 2-amino-substituted furans *e.g*., **8** have prompted us to report the synthesis of azaisobenzofuran **6**, the first highly stable functional analogue of **7**, by a Hamaguchi-Ibata[6,7] reaction.





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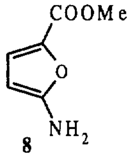

8

1, X=Y=Z=H
2, X=H; Y=Z=Me
3, X=H; Y=NPr^i_2; Z=H
4, X=Y=H; Z=NEt_2
5, X=H; Y=CO_2Me; Z=NEt_2
6, X=Cl; Y=CO_2Me; Z=NEt_2

The substituted diazoacetic ester **12** (mp 112-114°C; IR(KBr): 2113, 1714, 1634 cm^{-1}), the substrate for the Hamaguchi-Ibata reaction, was made from the readily available nitrile **9**[10] by standard synthetic protocol as shown in Scheme 1. When **12** was exposed to 1 mol% $Rh_2(OAc)_4$ in CH_2Cl_2 at room temperature for 1h the azaisobenzofuran **6** was obtained in 50% yield as a bright orange air and light-stable crystalline solid, which melted without decomposition at 110-112°C. The structure of **6**[14] is supported by its ^{1}H-NMR(300 MHz, $CDCl_3$) spectrum which displays signals at δ7.41(s, 1H), 3.90(s, 3H), 3.76(q, 4H, *J*=7.0Hz) and 1.35(t, 6H, *J*=7.0Hz). The ^{13}C-NMR spectrum is also consistent with the assigned structure.[14] The structure of **6** is further supported by its high reactivity in a Diels-Alder reaction (Scheme 2). When a dichloromethane solution of methyl acrylate (1.2 eq) was added to crystalline **6**, a single adduct **14**[15] (yellow plates, mp 150°C) was formed in almost quantitative yield *via* ring opening of **13** and subsequent proton transfer.

The unusual stability of **6** is attributable to resonance involving the pyridine nitrogen and to electron withdrawal by that nitrogen as well as the ester group. In fact, calculated heats of formation using the PM3 semi-empirical molecular orbital method[12] reveal how thermodynamic stability goes up in the series: **1**(27.20

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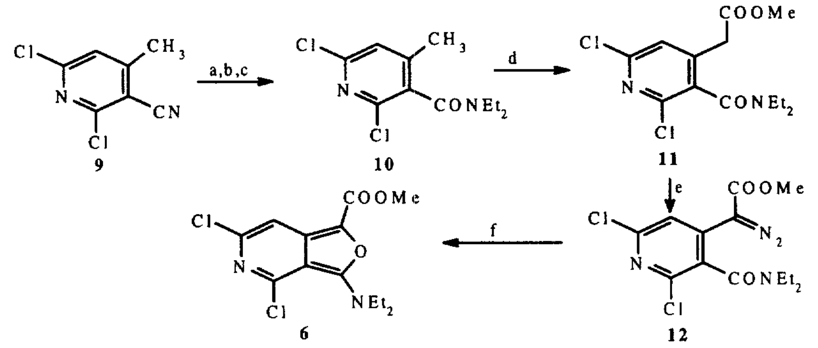
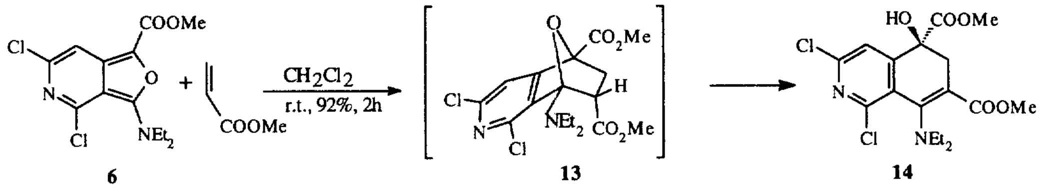
Scheme 1



a) DIBALH,CH_2Cl_2,-78^{0}C→r.t.,2h,66%. b) $NaClO_2$,^{t}BuOH,H_2O,78%. c) $(COCl)_2$,PhH, and then Et_2NH,py,64%.d) LDA,THF, and then $CO(OMe)_2$,53%. e) 4-Acetamidobenzenesulfonyl azide,Et_3N,0^{0}C→r.t.(ref.11),85% f) $Rh_2(OAc)_4$, CH_2Cl_2,r.t.,50%.

Scheme 2



kcal/mol) < 4(12.96 kcal/mol) < 5(-67.66 kcal/mol) < 6 (-77.69 kcal/mol). The observed regioselectivity in the cycloaddition of **6** with methyl acrylate is similar to that of **8**[9] and may be rationalized by FMO theory.[9,13] This is a normal demand $\pi4s+\pi2s$ process with a HOMO-LUMO gap of 8.51eV between the HOMO of **6** and LUMO of methyl acrylate. The analogous HOMO-LUMO gaps for **1**, **4** and **5** are 8.62, 7.95 and 8.22 eV, respectively. In addition, the atomic coefficients of the interacting orbitals *e.g.*, 0.27(ester carbon) and −0.10(amino carbon) of the $\pi4$ system (*e.g.*, **6**) match with 0.43 and −0.25 of the $\pi2$ acrylate system to provide **13** and the secondary orbital interaction which leads to assumed *endo* addition is also favourable.

In conclusion, the isolation and characterization of the stable azaisobenzofuran **6** conclusively establishes the intermediacy of such species in Hamaguchi-Ibata reactions. Further work involving inter- and intramolecular Diels-Alder and other reactions involving **6** and analogues leading to an array of heteroaromatic ring systems is currently underway in this laboratory.

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References & Notes

1) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. 2) Katritzky, A.R.; Rees, C.W.; Scriven,E.F.V. *Comprehensive Heterocyclic Chemistry*, Vol. 10. Pergamon Press, Oxford (1996). 3)Wiersum, U.E.; Eldred, C.D. *Tetrahedron Lett.* **1977**, *18*, 1741. 4) Muller, P.; Schaller, J-P. *Tetrahedron Lett.* **1989**, *30*, 1507. 5) Chen, C-W.; Beak, P. *J. Org. Chem.* **1986**, *51*, 3325. 6) Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1976**, 287. 7) For giving this reaction a name reaction status see: Peters, O.; Friedrichsen, W. *Tetrahedron Lett.* **1995**, *36*, 8581. 8) Carly, P.R.; Compernolle, F.; Hoornaert, G.J. *Tetrahedron Lett.* **1995**, *36*, 2113. 9) Padwa, A.; Dimitroff, M.; Wasterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088. See also Padwa, A.; Dimitroff, M.; Wasterson, A.G.; Wu, T. *J. Org. Chem.* **1998**, *63*, 3986. 10) Bobbitt, J. M.; Scola, D.A. *J. Org. Chem.* **1960**, *25*, 560. 11) Baum, J.S.; Shook, D.A.; Davies, H.M.L.; Smith, H.D. *Synth. Commun.* **1987**, *17*, 1709. 12) All calculations were done using the semi-empirical method PM3 implanted on Spartan with full geometry optimization. Stewart, J.J.P. *J. Comput. Aided Mol. Des.* **1990**, *4*, 1. 13) Fleming, I. *Frontier Orbitals and organic Chemical Reactions*, Wiley-Interscience, New York, 1976. 14) IR(KBr): 1679, 1609, 1568 cm^{-1}. ^{1}H-NMR(300MHz,$CDCl_3$): δ 7.41(s,1H), 3.90(s,3H), 3.76(q,4H,*J*=7.0Hz), 1.35(t, 6H, *J*=7.0Hz). ^{13}C NMR(300MHz,$CDCl_3$): δ 158.46(s), 157.16(s), 145.96(s), 144.63(s), 135.05(s), 122.65(s), 108.80(d), 102.14(s), 50.95(q), 46.30(t,2C), 12.95(q,2C). MS, m/e 318/316(M^+), 289/287($M-C_2H_5$), 261/259, 233/231, 201/199. 15) IR(KBr): 1742, 1674 cm^{-1}. ^{1}H-NMR(300MHz,$CDCl_3$): δ 7.47(s,1H) 3.72(s,3H), 3.66(s,3H), 3.26-3.15(m,2H), 3.05-2.93(m,3H), 2.81(d,1H,*J*=14.6Hz), 1.00(t,6H,*J*=7.1Hz). ^{13}C NMR(300MHz, $CDCl_3$): δ 172.60(s), 167.49(s), 156.13(s), 150.05(s), 148.06(s), 147.35(s), 126.07(s), 119.02(d), 104.66(s), 74.29(s), 53.50(q), 51.52(q), 45.74(t,2C), 37.90(t), 12.33(q,2C). MS, m/e 404/402(M^+), 389/387($M-CH_3$), 375/373($M-C_2H_5$), 369/367(M-Cl), 345/343($M-CO_2Me$).