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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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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. © 1998 Published by Elsevier Science Ltd. All rights reserved.

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 ¹H-NMR spectroscopy.⁴ Although not isolated, substituted isobenzofurans¹ 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 resurgence⁸ of interest in labile pyridine *o*-quinodimethanes *e.g.*, 7 and the appearance of a report⁹ 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.



1, X=Y=Z=H 2, X=H; Y=Z=Me 3, X=H; Y=NPrⁱ₂; Z=H 4, X=Y=H; Z=NEt 2 5, X=H; Y=CO₂Me; Z=NEt 2 6, X=Cl; Y=CO₂Me; 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% Rh₂(OAc)₄ in CH₂Cl₂ 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 6¹⁴ is supported by its ¹H-NMR(300 MHz, CDCl₃) spectrum which displays signals at $\delta7.41(s, 1H)$, 3.90(s, 3H), 3.76(q, 4H, J=7.0Hz) and 1.35(t, 6H, J=7.0Hz). The ¹³C-NMR spectrum is also consistent with the assigned structure.¹⁴ The structure of 6is 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 14¹⁵ (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 method¹² reveal how thermodynamic stability goes up in the series: 1(27.20)



a) DIBALH,CH₂Cl₂,-78⁰C \rightarrow r.t.,2h,66%. b) NaClO₂,^tBuOH,H₂O,78%. c) (COCl)₂,PhH, and then Et₂NH,py,64%.d) LDA,THF, and then CO(OMe)₂,53%. e) 4-Acetamidobenzenesulfonyl azide,Et₃N,0⁰C \rightarrow r.t.(ref.11),85% f) Rh₂(OAc)₄, CH₂Cl₂,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 $\pi 4s + \pi 2s$ 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 $\pi 4$ system (*e.g.*, 6) match with 0.43 and -0.25 of the $\pi 2$ 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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