Pergamon

Tetrahedron Letters 41 (2000) 5613–5616

TETRAHEDRON LETTERS

One-step synthesis of new heterocyclic azacyanines

Makhluf J. Haddadin,[a] Mark J. Kurth[b,*] and Marilyn M. Olmstead[b]

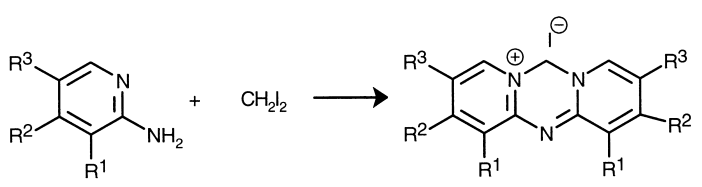
[a]*Department of Chemistry, American University of Beirut, Beirut, Lebanon*
[b]*Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616-5295, USA*

Received 12 April 2000; accepted 1 June 2000

Abstract

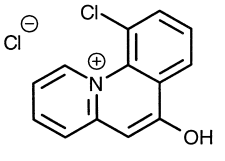
A wider scope of the one-step reaction of amino-substituted heterocycles with diiodomethane is demonstrated by the synthesis of a variety of novel pyridino, isoquinolino, benzimidazolo, and benzthiazoloazacyanines.

Interest in the coupling of a cyclic azapyridino moiety (**2**) to a conjugated polymeric backbone to yield polymers with potential superconducting properties led Munavalli, Hsu and Poziomek[1] to prepare a few derivatives of *N,N′*-methylene-2,2′-azapyridinocyanines (**2**) by the reaction of 2-aminopicolines (**1**) and diiodomethane. Although this reaction constitutes a one-step method for the preparation of what are otherwise difficult compounds to prepare, it appears to be of limited scope. Indeed, the authors[1] reported that reactions fail when an electron-withdrawing substituent is present on the pyridine ring; bromo and nitro substituents were cited. Furthermore, 'the reaction of 2-amino-substituted five-membered diheterocyclic compounds and diiodomethane failed' and only starting materials were recovered.



1 **2**

$R^1 = CH_3$, $R^2 = R^3 = H$
$R^2 = CH_3$, $R^1 = R^3 = H$
$R^3 = CH_3$, $R^1 = R^2 = H$



MPB-07

Becq's recent report[2] that the benzo[*c*]quinolizinium derivative MPB-07 activates wild-type CFTR, the cystic fibrosis transmembrane conductance regulator membrane protein,[3] in a variety

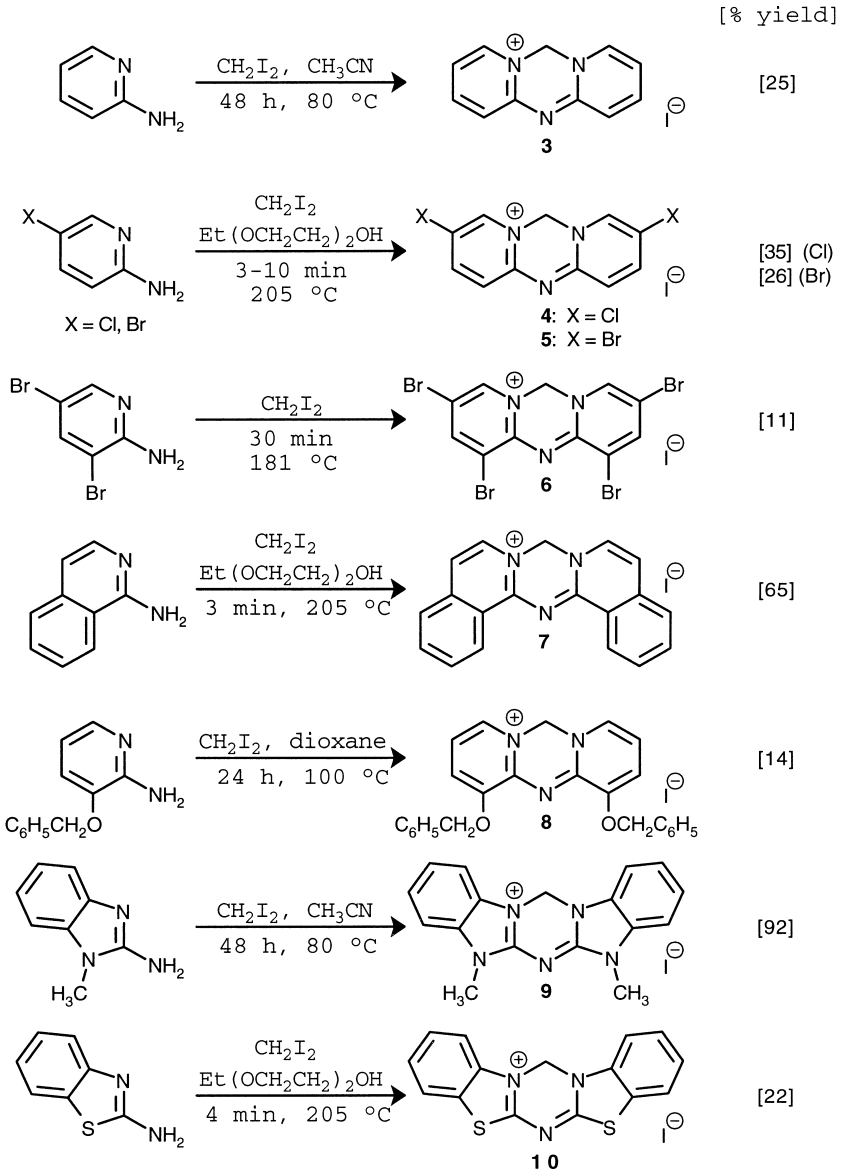
* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00908-4

of cell systems, coupled with our interests[4] in developing small molecule drugs capable of modulating chloride-selective ion channels[5] led us to explore the chemistry of azacyanines. We report here a wider perspective on the intriguing and useful reaction of amino-substituted heterocycles with diiodomethane.

The purpose of our study was to investigate the scope of π-sufficient and π-deficient 2-amino-heterocycles in their reactions with diiodomethane. As a starting point, we chose to establish the reactivity of the parent system, namely 2-aminopyridine, which has not been reported.[1] Munavalli reactions (**1**→**2**) were conducted at reflux in acetonitrile. Under these conditions (refluxing acetonitrile

Table 1
One-step azacyanine synthesis



or dioxane), we have found that 2-aminopyridine gives **3**, the parent compound, as a lemon yellow solid in 25% yield. In contrast to reported findings,[1] we were also gratified to find that 5-chloro- and 5-bromo-2-aminopyridines do react with diiodomethane to yield **4** (35%) and **5** (26%), respectively; albeit a significantly higher reaction temperature was required [160–200°C in diglyme or 2-(2-ethoxyethoxy)ethanol]. Although in appreciably lower yield, even the more π-deficient 3,5-dibromo-2-aminopyridine reacts to give tetrabromoazacyanine **6** (see Table 1). 2-Aminoisoquinoline reacts with diiodomethane to give **7** in good yield and the structure was confirmed by X-ray crystallography (Fig. 1a, numbering of X-ray structures is unrelated to systematic nomenclature). Finally, π-sufficient, but sterically hindered, 3-benzyloxy-2-aminopyridine reacts to give azacyanine **8**.

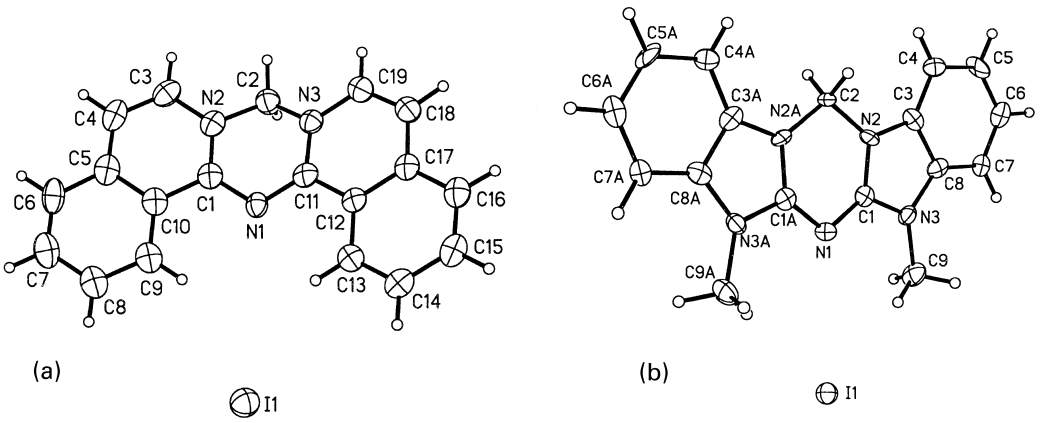


Figure 1. (a) X-Ray of **7**; (b) X-ray of **9**

In addressing the reactivity of five-membered π-sufficient heterocycles with two heteroatoms, we found that 1-methyl-2-aminobenzimidazole reacts smoothly with diiodomethane to give **9**. Under mild conditions (refluxing acetonitrile), this reaction affords a new 6,5,6,5,6-heterocyclic system with nitrogen as the only heteroatom. The structure of this novel compound, *N,N′*methylene-1,1′-dimethyl-2,2′-azadibenzimidazacyanine iodide (**9**; 92% yield), was established by IR and $^{1}H/^{13}C$ NMR and confirmed by X-ray crystallography (Fig. 1b). Another example of a reactive system containing a five-membered heterocycle is 2-aminobenzo-thiazole which delivers **10** (see Table 1) as a light yellow solid in 22% yield.

It is interesting to note that all of these azacyanines (**2**–**10**) are colored (straw to dark orange) and highly fluorescent. Because most of these reactions are conducted at elevated temperatures, significant decomposition of the starting 2-aminoheterocycle accompanies formation of product which appears as a precipitate. Attempts to increase the yield of reactions run at elevated temperatures resulted in a higher extent of starting material decomposition. The results presented here represent a tradeoff between higher yield versus purity and ease of reaction.

In conclusion, this report establishes that the Munavalli method for the preparation of heterocyclic azacyanines is of a wider scope than previously reported. Moreover, this reaction can lead to the synthesis not only of pyridinoazacyanines, but also to isoquinolino, benzimidazolo, and benzothiazoloazacyanines. Other aspects of the chemistry of this class of heterocycles will be communicated in due course.

Experimental example: Preparation of N,N′-methylene-1,1′-diisoquinolinoazacyanine Iodide (**7**). A solution of 2-aminoisoquinoline (0.72 g) and diiodomethane (3.6 g, excess) in 2(2-ethoxy-ethoxy)ethanol (2 mL) was refluxed for 3 min. The development of a dark brown solution was accompanied with the evolution of ammonia and a gradual appearance of the product as a solid. The mixture was allowed to cool to room temperature. The solid was dislodged with methanol (10 mL) and collected by suction filtration, washed with methanol (5 mL) and oven-dried (110°C), 0.65 g of bright orange solid (65% yield), m.p. >300°C. X-Ray crystals were obtained by recrystallization from MeOH–H_20. IR (strong bands) 1559, 1553, 1531, 1523, 1519, 1515, 1455, 1440, 1427, 788, 781, 689 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.97 (m, 2H), 7.88 (m, 8H), 6.61 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 151.2, 136.6, 134.7, 129.6, 126.9, 126.8, 122.8, 115.6, 65.1. The product is highly fluorescent: λ_{max} (excitation) in MeOH: 459, 685, 750 nm (the latter two broad peaks displayed an intensity of 400 and 370, respectively, at a concentration of 10^{-4} m/L). UV λ_{max} (MeOH): 454, 248, 232 nm ($\varepsilon = 2\times10^4$, 2.5×10^4 and 2.8×10^4, respectively). The structure of **7** was confirmed by X-ray crystallography (see text).

Acknowledgements

We are grateful to the National Science Foundation and the Cystic Fibrosis Foundation for financial support of this research. M.J.H. thanks the American University of Beirut for a sabbatical leave at the Univzersity of California, Davis. The 400 and 300 MHz NMR spectrometers used in this study were funded in part by a grant from NSF (CHE-9808183).

References

1. Munavalli, S.; Hsu, F.-L.; Poziomek, E. J. *Heterocycles* **1986**, *24*, 1893.
2. Becq, F.; Mettey, Y.; Gray, M. A.; Galietta, L. J.; Dormer, R. L.; Merten, M.; Metaye, T.; Chappe, V.; Marvingt-Mounir, C.; Zegarra-Moran, O.; Tarran, R.; Bulteau, L.; Dérand, R.; Pereira, M. M. C.; McPherson, M. A.; Rogier, C.; Joffre, M.; Argetn, B. E.; Sarrouilhe, D.; Kammouni, W.; Figarella, C.; Verrier, B.; Gola, M.; Verfond, J.-M. *J. Biol. Chem.* **1999**, *39*, 27415.
3. (a) Riordan, J. R.; Rommens, J. M.; Kerem, B. S.; Alon, N.; Rozmahel, R.; Grzelczak, Z.; Zeilenski, J.; Lok, S.; Plavsic, N.; Chou, J. et al. *Science* **1989**, *245*, 1066. (b) Kerem, B.; Rommens, J. M.; Buchanan, J. A.; Markiewicz, D.; Cox, T. K.; Chakravarti, A.; Buchwald, M.; Tsui, L. C. *Science* **1989**, *245*, 1073.
4. Eda, M.; Kurth, M. J.; Nantz, M. H. *J. Org. Chem.* manuscript submitted.
5. Li, M.; MacCann, J. D.; Anderson, M. P.; Clancy, J. P.; Liedtke, C. M.; Nairn, A. C.; Greengard, P.; Welssch, M. J. *Science* **1989**, *244*, 1353.