JOC*Note*

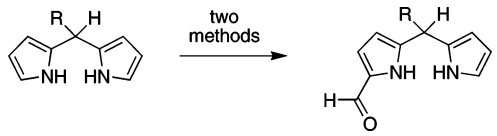
Synthesis of 1-Formyldipyrromethanes

Marcin Ptaszek, Brian E. McDowell, and Jonathan S. Lindsey*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

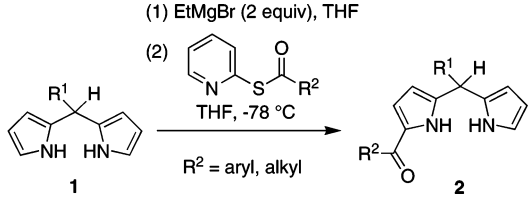
jlindsey@ncsu.edu

Received January 19, 2006



1-Formyldipyrromethanes are versatile precursors to porphyrins and chlorins. Two methods of synthesis of 1-formyldipyrromethanes have been investigated: (1) Vilsmeier formylation followed by selective removal of the unwanted 1,9-diformyldipyrromethane by dialkyltin complexation and (2) reaction with mesitylmagnesium bromide (MesMgBr) followed by formylation with phenyl formate. The two approaches are complementary (acidic versus basic conditions; statistical versus selective formylation). The latter was found to be more efficient for the preparation of 1-formyldipyrromethanes.

The rational synthesis of substituted porphyrins and chlorins relies heavily on dipyrromethane building blocks (**1**).[1,2] The desired reactivity of dipyrromethanes is attained by the introduction of functional groups at the 1- and 9-positions. Because such α-pyrrolic positions exhibit high reactivity toward electrophiles, 1,9-difunctionalization (acylation,[1] aminomethylation,[3] bromination,[4] chlorination,[5] and formylation[6,7]) of dipyrromethanes can be done in a relatively straightforward manner. A more challenging task is the selective synthesis of 1-substituted dipyrromethanes, given the comparable reactivity of the 1- and 9-positions. Indeed, treatment of a dipyrromethane with an equimolar amount of an electrophilic reagent usually results in a statistical mixture of unreacted starting material, the desired 1-substituted product, and the 1,9-disubstituted derivative. We previously developed a method for selective 1-acylation of dipyrromethanes, employing a *S*-2-pyridyl thioate (Mukaiyama reagent) as an acylating agent for use with the magnesium salt of the dipyrromethane (eq 1).[8] On the other hand, no methods for selective 1-formylation of dipyrromethanes have been developed. Battersby reported a rational, albeit lengthy, six-step synthesis of 1-formyldipyrromethane (**2a**) by using *N*-mesyl 2-chloromethylpyrrole and an acetal of pyrrole-2-carboxaldehyde as building blocks.[9] The most direct method at present for preparing 1-formyldipyrromethanes entails statistical Vilsmeier formylation of a dipyrromethane followed by extensive chromatography. Here, we report two simple methods for more expeditious syntheses of 1-formyldipyrromethanes.



(1)

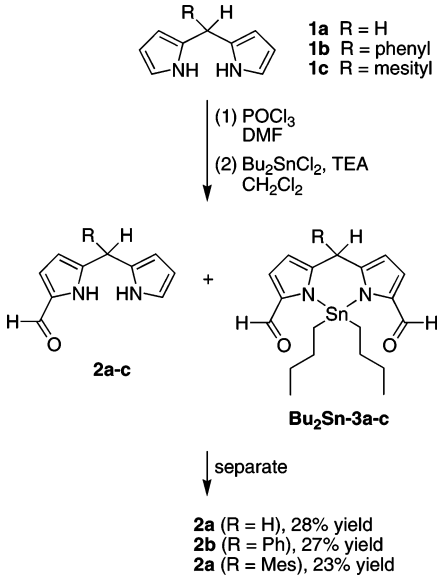
A. Statistical Vilsmeier Formylation and Selective Complexation. Treatment of dipyrromethane (**1a**)[10] with the Vilsmeier reagent afforded the expected mixture of the 1-formyldipyrromethane (**2a**) and 1,9-diformyldipyrromethane (**3a**) (Scheme 1). To facilitate separation of the formyldipyrromethane species, the mixture was treated with Bu_2SnCl_2 and TEA in CH_2Cl_2 at room temperature. The tin-complexation process[11] is selective for the 1,9-diformyl species, yielding a hydrophobic 1,9-diformyldipyrromethane−dibutyltin complex (**Bu_2Sn-3**)[12] and the uncomplexed 1-formyldipyrromethane. The mixture was separated by flash chromatography to afford the desired 1-formyldipyrromethane **2a**. Similar treatment of dipyrromethane **1b** or **1c** afforded 1-formyldipyrromethane **2b**[6,13] or **2c**. This procedure proved viable for small-scale preparations, but partial decomplexation upon chromatographic separation limited larger scale implementation (see the Supporting Information).

B. Selective Formylation. 1. Survey of Routes. Several approaches were explored to achieve selective formylation. Attempts to decrease the reactivity of one of the pyrrole rings in the dipyrromethane by selective *N*-tosylation of the dipyrromethane, or preparation of an *N*-tosylated dipyrromethane from *N*-tosylpyrrole, were unsuccessful, although an *N*-mesylpyrrole was used in the rational synthesis of 1-formyldipyrromethane.[9] The rational synthesis of 1-acyldipyrromethanes, which entails acylation of the magnesium salt of the dipyrromethane with an appropriate *S*-2-pyridyl thioate, works well with aryl or alkyl substituents (eq 1).[8] However, attempts to extend this method to include 1-formylation were thwarted because we were unable to prepare the requisite pyridyl thioformate. Thus, the

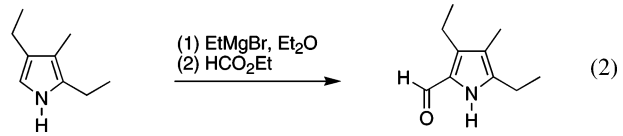
(1) Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323−7344.
(2) Taniguchi, M.; Ra, D.; Mo, G.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2001**, *66*, 7342−7354.
(3) Fan, D.; Taniguchi, M.; Yao, Z.; Dhanalekshmi, S.; Lindsey, J. S. *Tetrahedron* **2005**, *61*, 10291−10302.
(4) Strachan, J.-P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 3160−3172.
(5) Rohand, T.; Baruah, M.; Qin, W.; Boens, N.; Dehaen, W. *Chem. Commun.* **2006**, 266−268.
(6) Brückner, C.; Posakony, J. J.; Johnson, C. K.; Boyle, R. W.; James, B. R.; Dolphin, D. *J. Porphyrins Phthalocyanines* **1998**, *2*, 455−465.
(7) (a) Sessler, J. L.; Seidel, D.; Bucher, C.; Lynch, V. *Tetrahedron* **2001**, *57*, 3743−3752. (b) Wickramasinghe, A.; Jaquinod, L.; Nurco, D. J.; Smith, K. M. *Tetrahedron* **2001**, *57*, 4261−4269.
(8) Rao, P. D.; Littler, B. J.; Geier, G. R., III; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 1084−1092.
(9) Abell, A. D.; Nabbs, B. K.; Battersby, A. R. *J. Org. Chem.* **1998**, *63*, 8163−8169.
(10) Laha, J. K.; Dhanalekshmi, S.; Taniguchi, M.; Ambroise, A.; Lindsey, J. S. *Org. Process Res. Dev.* **2003**, *7*, 799−812.
(11) Tamaru, S.-I.; Yu, L.; Youngblood, W. J.; Muthukumaran, K.; Taniguchi, M.; Lindsey, J. S. *J. Org. Chem.* **2004**, *69*, 765−777.
(12) Taniguchi, M.; Balakumar, A.; Fan, D.; McDowell, B. E.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2005**, *9*, 554−574.
(13) Briñas, R. P.; Brückner, C. *Tetrahedron* **2002**, *58*, 4375−4381.

10.1021/jo060119b CCC: $33.50
Published on Web 04/15/2006

SCHEME 1



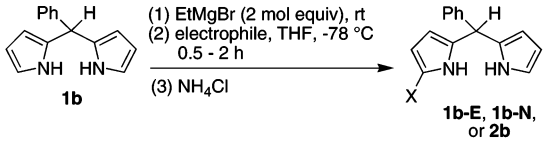
application of methods developed for the synthesis of thioformates[14] with pyridyl-2-thiol and (1) formyl acetate or (2) formic acid and DCC failed to give *S*-2-pyridyl methanethioate. On the other hand, Fischer's formylation of alkylpyrroles by reaction of the pyrrole−Grignard reagent with ethyl formate (eq 2)[15] prompted us to examine a broad selection of formylating agents for the Grignard-mediated formylation of a dipyrromethane.

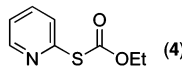
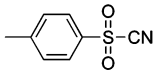


(2)

As a first approach, we considered the selective introduction of latent formyl synthons. Thus, reaction of ethyl chloroformate with 2-mercaptopyridine afforded the Mukaiyama reagent *O*-ethyl *S*-2-pyridyl carbonothioate (**4**) in 92% yield. Reaction of **4** and **1b** under standard conditions (treatment of **1b** with 2 molar equiv of EtMgBr at room temperature and then with **4** at −78 °C in THF) afforded 1-(ethoxycarbonyl)dipyrromethane **1b-E** in 45% yield (Table 1, entry 1). However, reduction of **1b-E** with DIBAL-H at −78 °C (in THF or CH_2Cl_2) afforded the corresponding alcohol without any detected aldehyde. Alternatively, treatment of **1b** with EtMgBr followed by *p*-tosyl cyanide[16] afforded 1-cyanodipyrromethane **1b-N** in 31% yield, together with an unidentified byproduct (putative 3-cyanodipyrromethane). The difficulty in separating **1b-N** from the byproduct made this route unattractive (entry 2). Following Fischer's approach, reaction of **1b** with EtMgBr followed by methyl formate afforded the desired **2b** in 20% yield, accompanied by several byproducts (entry 3). Attempts to improve the yield and purity failed: the reaction in toluene instead of THF gave essentially the same results, whereas reaction at −78 °C for 15 min rather than 1 h, or use of 1 mol equiv of EtMgBr, resulted

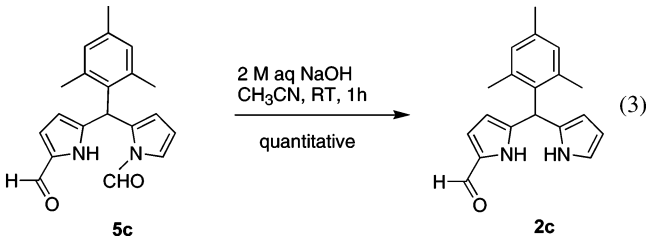
TABLE 1. Examination of Electrophiles for Dipyrromethane Substitution



Entry	Electrophile	Product	X	Yield
1	 (4)	**1b-E**		45%
2		**1b-N**		31%
3	HCO_2Me	**2b**		20%
4	DMF	**2b**		0%

in recovery of starting material. The reaction of the magnesium salt of **1b** with DMF at −78 °C provided unreacted starting material (entry 4). The use of 2-cyanoethyl formate as formylating agent also gave no improvement.

Upon examining the reaction mixture obtained with methyl formate (entry 3), a significant byproduct was found to be the 1,11-diformyldipyrromethane (**5**). This product is dominant when the formylating reagent is added to the magnesium salt of the dipyrromethane at 0 °C. We found that the *N*-formyl group could be smoothly and quantitatively hydrolyzed by treatment with 2 M aqueous NaOH as illustrated in eq 3.[17] Thus, treatment of **1b** with EtMgBr and methyl formate gave the crude mixture of **2b** and **5b** (accompanied by several minor, unidentified byproducts), which upon treatment with 2 M aqueous NaOH followed by column chromatography gave **2b** in 28% yield.



(3)

Additional refinements to the formylation method entailed use of MesMgBr rather than EtMgBr[18] and phenyl formate rather than methyl formate. Thus, the standard formylation method entailed treatment of a solution of dipyrromethane in THF at room temperature with 2 molar equiv of MesMgBr and then at −78 °C with 2 molar equiv of phenyl formate. After 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the crude mixture was treated with 2 M aqueous NaOH. The 1-formyldipyrromethane was isolated using column chromatography.

2. Scope. We applied the refined procedure with 11 dipyrromethanes bearing various 5-substituents (Table 2). Dipyrromethanes **1a**−**e**,[10] **1f**,[19] **1g**,[18] **1h**,[19] **1i**,[1] **1j**,[20] and **1k**[21] were

(14) (a) Pohl, E. R.; Hupe, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 2763−2768. (b) Sprecher, M.; Nov, E. *Synth. Commun.* **1992**, *22*, 2949−2954.

(15) Fischer, H.; Siedel, W.; Le Thierry d'Ennequin, L. *Liebigs Ann.* **1933**, *500*, 137−202.

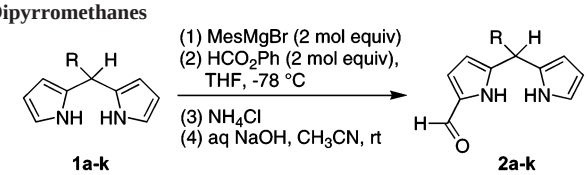
(16) Nagasaki, I.; Suzuki, Y.; Iwamoto, K.-I.; Higashino, T.; Miyashita, A. *Heterocycles* **1997**, *46*, 443−450.

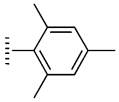
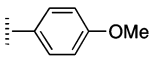
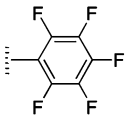
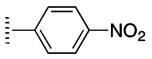
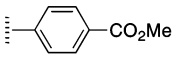
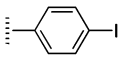
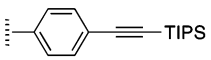
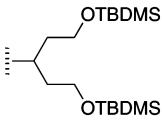
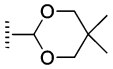
(17) Bergauer, M.; Gmeiner, P. *Synthesis* **2001**, 2281−2288.

(18) Zaidi, S. H. H.; Loewe, R. S.; Clark, B. A.; Jacob, M. J.; Lindsey, J. S. *Org. Process Res. Dev.* **2006**, *10*, 304−314.

(19) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391−1396.

TABLE 2. Scope of Grignard-Mediated 1-Formylation of Dipyrromethanes



DPM	R group	1-Formyl DPM	Yield
1a	–H	2a	32%
1b		2b	37%
1c		2c	32%
1d		2d	38%
1e		2e	28%
1f		2f	0%
1g		2g	--[a]
1h		2h	34%
1i		2i	38%
1j		2j	57%
1k		2k	65%

[a] Product was observed but not isolated (see text).

prepared as described in the literature. In each application of the formylation procedure, no 1,9-diformyldipyrromethane was detected. The formylation method gave yields of 28−65% with only two failures: (1) 5-(4-Nitrophenyl)dipyrromethane (**1f**) gave a dark, tarry mixture upon addition of MesMgBr, and the desired 1-formyldipyrromethane was not obtained upon treatment with phenyl formate. (2) 5-(4-Methoxycarbonylphenyl)-dipyrromethane (**1g**) afforded the desired monoformyl product together with the corresponding 1,11-diformyldipyrromethane (as determined by ^{1}H NMR analysis of the crude reaction mixture), but attempts to hydrolyze the crude mixture gave multiple products, probably owing to ester hydrolysis. The yields were ∼30% for dipyrromethanes bearing a 5-aryl or 5-H substituent, whereas yields of ∼60% were obtained for the two dipyrromethanes bearing a 5-alkyl substituent. The formylation procedure was scaled up with 50 mmol of **1b**, affording 4.5 g of **2b** (36% yield).

In summary, the two methods for 1-formylation are complementary both in conditions (acidic versus basic) and in selectivity (statistical Vilsmeier versus directed Grignard reaction). The Grignard-mediated reaction is particularly attractive owing to its simplicity, lack of formation of 1,9-diformyldipyrromethane, and broad scope. The yields with nine dipyrromethanes ranged from 28% to 65% and encompassed a variety of moieties including alkyl, aryl, ether, dioxane, silyl ether, alkyne, iodo, and pentafluorophenyl.

Experimental Section

General Procedure for Vilsmeier Formylation and Tin Complexation, Exemplified for 1-Formyldipyrromethane (2a). Following a procedure for the formylation of dipyrromethanes,[6] DMF (10 mL) was treated with $POCl_3$ (1.50 mL, 16.4 mmol) at 0 °C under argon, and the resulting solution was stirred for 10 min (Vilsmeier reagent). A solution of **1a** (1.00 g, 6.84 mmol) in DMF (23 mL) at 0 °C under argon was treated with the freshly prepared Vilsmeier reagent (5.16 mL, 1.08 mol equiv), and the resulting solution was allowed to stir for 1.5 h at 0 °C. Saturated aqueous sodium acetate solution (76 mL) was added, and the ice bath was removed. The mixture was then stirred for 4 h and allowed to warm to room temperature. The mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated to afford a brown oil. Following a procedure for the dialkyltin complexation of 1,9-diacyldipyrromethanes,[11] the crude oil was dissolved in CH_2Cl_2 (34 mL) and treated with TEA (2.85 mL, 20.5 mmol) and Bu_2SnCl_2 (2.08 g, 6.84 mmol). The mixture was stirred for 30 min at room temperature. The solvent was removed. The resulting oil was chromatographed [silica, hexanes/ethyl acetate (9:1 to 1:1) containing 1% TEA] to afford a brown solid (338 mg, 28% overall): mp 115−116 °C (lit.[9] mp 118 °C); ^{1}H NMR δ 4.04 (s, 2H), 6.06−6.13 (m, 1H), 6.14−6.18 (m, 2H), 6.70−6.72 (m, 1H), 6.93−6.95 (m, 1H), 8.62 (br s, 1H), 9.36 (s, 1H), 10.07 (br s, 1H); ^{13}C NMR δ 26.9, 106.9, 108.7, 110.9, 117.9, 124.9, 127.7, 132.4, 142.5, 179.1. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.72; H, 5.77; N, 15.97.

General Procedure for the Grignard-Mediated Formylation (Applied to 2a−i), Exemplified for 1-Formyl-5-phenyldipyrromethane (2b). A sample of **1b** (1.11 g, 5.00 mmol) in THF (10 mL) was treated with MesMgBr (10.0 mL, 1 M in THF, 10 mmol). After 10 min, the mixture was cooled to −78 °C. Phenyl formate (1.09 mL, 10.0 mmol) was added in one portion. The reaction mixture was stirred at −78 °C for 1 h. The cooling bath was removed, and stirring was continued for 1 h. The reaction was quenched by adding saturated aqueous NH_4Cl (∼30 mL). The resulting mixture was extracted with CH_2Cl_2. The organic extract was washed (water, brine) and concentrated. The resulting oil was dissolved in CH_3CN (30 mL) and treated with 2 M aqueous NaOH (30 mL). The resulting mixture was stirred vigorously at room temperature for 1 h. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was washed (saturated aqueous NH_4Cl, water, brine), dried (Na_2SO_4), and concentrated. The resulting dark oil was chromatographed [silica, CH_2Cl_2 to CH_2Cl_2/ethyl acetate (10:1)] to afford a light brown powder (0.457 g, 37%). The characterization data (^{1}H NMR and FAB-MS spectra) were consistent with those obtained for the title compound prepared via Vilsmeier formylation (see the Supporting Information).

Grignard-Mediated Synthesis (50 mmol Scale) of 1-Formyl-5-phenyldipyrromethane (2b). A sample of **1b** (11.1 g, 50.0 mmol) in THF (100 mL) in a 500 mL round-bottomed flask was

(20) Borbas, K. E.; Mroz, P.; Hamblin, M. R.; Lindsey, J. S. *Bioconjugate Chem.* **2006**, *17*, in press.
(21) Balakumar, A.; Muthukumaran, K.; Lindsey, J. S. *J. Org. Chem.* **2004**, *69*, 5112−5115.

treated with MesMgBr (100 mL, 100 mmol, 1 M in THF). After 10 min, the mixture was cooled to −78 °C. Phenyl formate (10.9 mL, 100 mmol) was added in one portion. The reaction mixture was stirred at −78 °C for 1 h. The cooling bath was removed, and stirring was continued for 1 h. The reaction was quenched by adding saturated aqueous NH_4Cl (∼200 mL). The resulting mixture was extracted with CH_2Cl_2. The organic extract was washed (water, brine) and concentrated. The resulting oil was dissolved in CH_3CN (150 mL) and treated with 2 M aqueous NaOH (150 mL). The resulting mixture was stirred vigorously at room temperature for 1 h. Water (∼200 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was washed (saturated aqueous NH_4Cl, water, brine), dried (Na_2SO_4), and concentrated. The resulting dark oil was chromatographed [silica, 7 × 26 cm, total 440 g, CH_2Cl_2 to CH_2Cl_2/ethyl acetate (10:1), total volume ∼6 L] to afford a gray-yellow powder (4.55 g, 36%). The characterization data (^{1}H NMR spectrum and elemental analysis) were consistent with those obtained for the title compound prepared via Vilsmeier formylation (see the Supporting Information).

Acknowledgment. This research was supported by the NIH (GM-36238). Mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology at North Carolina State University. Partial funding for the facility was obtained from the North Carolina Biotechnology Center and the National Science Foundation.

Supporting Information Available: Complete Experimental Section including procedures for the synthesis of all new compounds; NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060119B