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Regioselective electrophilic formylation — 3-substituted thiophenes as a case study

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Abstract

A variety of methods for regioselective formylation have been examined and exemplified with 3-methylthiophene. Optimal yields and regioselectivity for 2-formylation were obtained with *N*-formylpyrrolidine (11:1) although up to a 46:1 ratio could be obtained with $MeOCHCl_2$:$TiCl_4$, albeit in lower yield. Optimal 5-formylation (1:1.5) was obtained when using *N*-formylindoline:$(COCl)_2$.

Formylation is a key process in organic synthesis, with the resulting aldehyde function being a 'crossroads' intermediate. Not surprisingly, a large number of methods have been developed for this reaction. Reagents for electrophilic formylation[1] are mostly of the form $Y–CH=X^+$. Thus, the reactions attributed to Vilsmeier ($ClCH=NR_2^+$), Rieche (e.g. $MeOCHCl_2 \rightarrow MeO=CHCl^+$), Gatterman ($Zn[CN]_2/HCl \rightarrow HC=NH_2^{2+}$), Gatterman–Koch ($CO/HCl/Lewis\ acid \rightarrow HC=O^+$) and even Duff ($CH_2=NH_2^+$ — followed by dehydrogenation of initially formed RCH_2NH_2) all fit this pattern. The difference between these reagents lies primarily in: (i) their reactivity; *O*-based reagents more reactive than *N*-based ones; and (ii) their steric bulk. From a regioselectivity viewpoint the more reactive systems would be expected to be less selective while a sterically bulky reagent should favour the least hindered site of reaction (and vice versa).

Some limited work has been published on the regioselectivity of electrophilic formylation. Thus, Vilsmeier formylation of anisole gives 89:11 (58%) of 4- to 2-isomers with $DMF/POCl_3$ but 94:6 (75%) when the bulkier pyrophosphoryl chloride is used, with this rising to >98:2 (72%) when *N*-methylformanilide replaces the DMF.[2] Some work has been reported by Detty and Hays[3] on the $DMF/POCl_3$ formylation of 3-alkylthiophenes (a ratio of 2:5 substitution using 3-Me, Et, *n*-Pr, *i*-Pr and *n*-Bu derivatives were 6.1, 2.85, 3.55, 1.1, and 2.7 to 1, respectively) while using *N*-methylformanilide (NMFA) gave ratios of 3.0, 2.0, 1.8, 1.8 and 0.7 to 1, respectively. The effect of the increasing size of the Vilsmeier amide is clearly evident, with the bulkier NMFA giving up to a two-fold improvement in regioselection.

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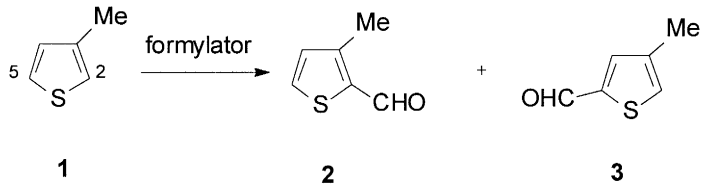
We herein examine the role of the bulk of the formylating agent in the formylation of 3-methylthiophene by examining the ratio of the product 2- to 5-formyl isomers (**2** and **3**) (Scheme 1).



1 **2** **3**

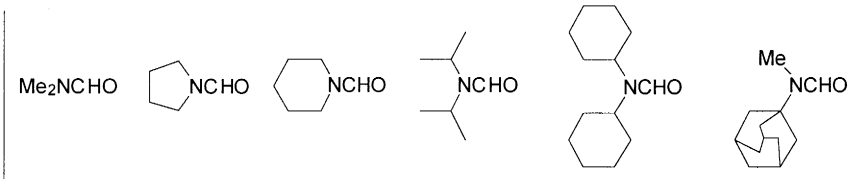
Scheme 1.

1. Formylation of 3-MT utilizing Vilsmeier reagents

Using Vilsmeier reagents[4] the bulk of the amide in particular and of the reagent in general is examined, using 3-methylthiophene (3-MT) **1** as the substrate. There is much demand for regioselectively formylated 3-MT as a veterinary drug intermediate.

Table 1 shows the effect of decreasing (*N*-formylpyrrolidine) and increasing the size of Vilsmeier aliphatic amides compared to DMF, the most commonly employed reagent. A 4.5-fold change in regioselection is observed. Globular systems (adamantyl) seem to convey little extra benefit. Clearly, for optimal 2-formylation *N*-formylpyrrolidine is the best Vilsmeier amide, while dicyclohexylformamide confers maximum 5-selectivity.

Table 1
Vilsmeier formylation of 3-MT (**1**) using aliphatic amides $R_2NCHO/POCl_3$

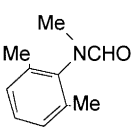
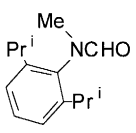
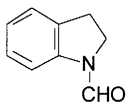
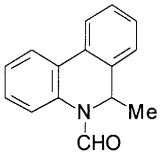


Yield (%)	85	78	84	61	61	16
2/**5** ratio	6.5	11	5.8	3.2	2.5	4.8

Aromatic Vilsmeier amides prove much more effective in ensuring optimal 5-formylation, the steric bulk conferred by one benzene ring being almost equivalent to that of two cyclohexyl rings (Table 2). Unfortunately, *N*-formyldiphenylamine is not effective as a Vilsmeier amide. Surprisingly, loading the phenyl ring with extra *ortho*-substituents *decreases* the regioselectivity slightly, no doubt due to the enforced orthogonality of the aromatic ring. When planarity of the ring was fixed by use of *N*-formylindoline, optimal 5-selectivity was observed. However, this is a rather sensitive amide to the usual $POCl_3$, and we utilized the milder acid halide, oxalyl chloride. Unfortunately, bulkier planar formamides such as *N*-formylcarbazole, -tetrahydrocarbazole, -hexahydrocarbazole or -2-methylindoline

proved ineffective Vilsmeier amides and the non-planar but buckled 5-methyl-5,6-dihydrophenanthridine conferred no extra selection.

Table 2
Vilsmeier formylation of 3-MT (**1**) using aromatic amides $R_2NCHO/POCl_3$

	Me_2NCHO	PhNMeCHO				
Yield (%)	85	78	70	20	47[a]	22
2/5 ratio	6.5	2.5	3	3	1.5[a]	3

Footnote: [a] Vilsmeier reagent made using $(COCl)_2$ instead of $POCl_3$.

Varying the bulk of the Vilsmeier leaving group X in $R_2N{=}CHX^+$ (X=Cl, $OPOCl_2$, CF_3SO_3) by use of $(COCl)_2$, $O(POCl_2)_2$, or $(CF_3SO_2)_2$ as the Vilsmeier acylating agent had only a very small effect on the regioselection (6.3, 6.1, 5.8), suggesting quite reasonably that the Vilsmeier leaving group is *trans* to the largest *N*-substituent.

2. Formylation of 3-MT utilizing Rieche reagents

It is evident from the above results that Vilsmeier reagents are sterically bulky formylating agents. In order to improve 2-formylation selectivity further we therefore examined the more reactive but sterically less demanding Rieche reagents (e.g. $MeOCHCl_2 \rightarrow MeO{=}CHCl^+$). A Lewis acid such as $TiCl_4$ is required to convert the covalent equivalent of the Vilsmeier reagent into the active ionic agent. Table 3 records some of our results.[5] In brief, the regioselectivity was excellent but the overly vigorous reagent tended to destroy some of the 3-methylthiophene, making reproducibility a problem. Yields and product ratios were thus variable and are unreliable. No product was observed using BF_3, $ZnCl_2$, $Hf(OTf)_4$, $Yb(OTf)_3$ or $FeCl_3$ as Lewis acid.

Rieche's reagent should prove optimally regioselective in the formylation of more stable substrates. Thus, using 3-bromothiophene, formylation at −12°C using $TiCl_4$ gave the formyl-3-bromothiophene in 83% yield and with a 94:1 ratio of 2- to 5-isomers.

Finally, we have also investigated other bulkier but perhaps milder analogues of $MeOCHCl_2$ as formylating agents. The bromo-analogue ($MeOCHBr_2$) and thio-analogue ($MeSCHCl_2$) both gave only tarry products with 3-MT.

In conclusion, we have shown that regioselective formylation of 3-substituted thiophenes may be optimized by either: (i) utilizing small (→2-isomer) or large planar, aromatic Vilsmeier reagents (→5-isomer); or (ii) by utilizing the much smaller but more reactive Rieche reagents (→2-isomer). This methodology is now being applied to other regioselection problems.

Table 3
Rieche formylation of 3-MT (**1**) using $MeOCHCl_2$/Lewis acid/CH_2Cl_2

Lewis Acid:	$TiCl_4$	$TiCl_4$	$TiCl_3OPr^n$	$TiCl_2(OPr^n)_2$	$SbCl_5$	$InCl_3$[a] $ZrCl_4$
Temp. (^{0}C):	-5	-12	-12	-12	-17	-12
Yield (%):	27	52	36	10	13	7	20
Ratio **2**/**5**:	48	46	34	>99	23	90	18

Footnote: All reactions were conducted with 0.024M 3-MT, 0.02M $MeOCHCl_2$ and 0.04M Lewis acid, the Lewis acid being added dropwise to the other reactants. [a] Nitromethane used as solvent and 0.023M $InCl_3$.

Acknowledgements

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References

1. For a useful overview and leading references, see: March, J. *Advanced Organic Chemistry*, 4th edn; Wiley-Interscience: New York, 1992; 542.
2. Downie, I. M.; Earle, M. J.; Heaney, H.; Shuhaibar, K. F. *Tetrahedron* **1993**, *49*, 4015–4034.
3. Detty, M. R.; Hays, D. S. *Heterocycles* **1995**, *40*, 925–937.
4. *Typical conditions for Vilsmeier formylation*: To *N*-methylformanilide (1.49 g, 0.011 M) was added $POCl_3$ (5.0 mL) dropwise with ice-bath cooling and stirring. After 5 min heating at 80°C, 3-methylthiophene (0.98 g, 0.96 mL, 0.010 M) was added and the solution heated for 2 h at 80°C. The mixture was poured onto ice–water, basified (sat. aqueous K_2CO_3 solution) and extracted with CH_2Cl_2 (4×30 mL) washed, dried ($MgSO_4$) and evaporated, and the residue distilled on a Kugelrohr at ~135°C/10 mm.
5. *Typical conditions for Rieche formylation*: To a mixture of 3-methylthiophene (2.36 g, 2.32 mL, 0.024 M) and methyl dichloromethyl ether (2.98 g, 2.35 mL, 0.026 M) in dry CH_2Cl_2 (15 mL) at −12°C was added $TiCl_4$ (7.59 g, 4.39 mL, 0.04 M) dropwise over 40–50 min with stirring. After an additional 1 h at this temperature, water (30mL) was carefully added dropwise over 15 min and stirring continued for 30 min. Extraction of the aqueous phase with more CH_2Cl_2 (3×30 mL) and drying of the combined organic phase, afforded a product which was further worked up as above.