Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c6ob02727j

Received 25th November 2016,
Accepted 14th December 2016

DOI: 10.1039/c6ob02727j

www.rsc.org/obc

Formylation of phenols using formamidine acetate†

S. Hessam M. Mehr,[a] Hannah Depmeier,[a,b] Katsuya Fukuyama,[c] Mahboobeh Maghami[a] and Mark J. MacLachlan*[a]

We report a new method to formylate phenol derivatives using formamidine acetate and acetic anhydride. This general-purpose transformation is a significant improvement over many other methods and does not require high temperatures or the addition of strong acid or base. Mono-, di-, and tri-formylated product can be obtained, depending on the substrate and conditions used.

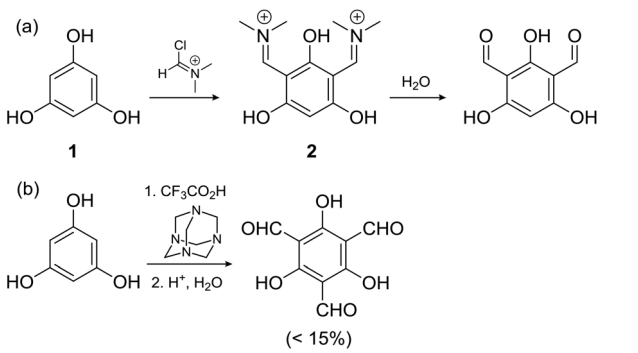
Aromatic aldehydes are convenient building blocks in synthetic and materials chemistry as well as for pharmaceuticals and biological systems. They are highly valued as intermediates in chemistry, thanks to their excellent reactivity toward nucleophiles and redox reagents.[1,2] The facile activation of aldehydes has enabled many of their applications, such as their use in self-assembled macrocycles[3–7] and covalent organic frameworks (COFs).[8–14] This versatility comes at a price, however, as their preparation is often complicated by the fragile nature of the aldehyde product.

The above limitation is particularly troubling in the transformation of phenols to salicylaldehydes, where oxidation reactions often lead to substrate degradation. Further, syntheses based on metalation require protection and deprotection of the hydroxyl groups. Hence, direct formylation of phenols is often only possible through electrophilic aromatic substitution.

Whereas ketone analogues of salicylaldehydes are easily prepared using Friedel–Crafts acylation, the same methodology cannot be used in the case of aldehydes since formyl halides and the putative formylium ion, HCO^+, both decompose with the formation of carbon monoxide. This instability can be overcome by using HCN as a CO surrogate, as in the Gattermann reaction, but the toxic reagent and harsh conditions required make the Gattermann reaction impractical. Furthermore, the familiar Reimer–Tiemann reaction[15,16] often yields large amounts of non-aromatic, ring-expanded, and polymeric side products, resulting in poor yield of formylated product.[17] Finally, the otherwise efficient preparation of salicylaldehydes from phenols and paraformaldehyde reported by Casnati *et al.*,[18] Casiraghi *et al.*[19] and Skattebøl[20] has not proven effective in introducing more than one formyl group on an aromatic ring.

State-of-the-art formylation methods rely on iminium species as a stable equivalent to formyl electrophiles. Best known among these is the Vilsmeier–Haack reaction,[21,22] where a chloroiminium intermediate acts as formylating agent, Scheme 1a. The deactivating, positively-charged iminium intermediate, *e.g.* **2**, produced in this reaction limits its ability to produce multiple formylations in a single step.[23] Substrate deactivation, along with the use of highly reactive $POCl_3/SOCl_2$ reagent, can also result in the formation of chlorinated side-products.[24–26]

The Duff reaction,[27–30] Scheme 1b, mitigates the deactivating effect of iminium substituents by initially introducing them as aminomethyl groups that are subsequently



Scheme 1 Vilsmeier–Haack (a) and Duff (b) formylation of phloroglucinol, **1**.

[a]*Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1, Canada. E-mail: mmaclach@chem.ubc.ca*
[b]*Department of Pharmaceutical Chemistry, Technische Hochschule Köln, CHEMPARK, Kaiser-Wilhelm-Allee, 51368 Leverkusen, Germany*
[c]*Center for Liberal Arts, Meiji Gakuin University, Yokohama 244-8539, Japan*

†Electronic supplementary information (ESI) available: Detailed formylation procedure, purification steps and full characterization of products. See DOI: 10.1039/c6ob02727j

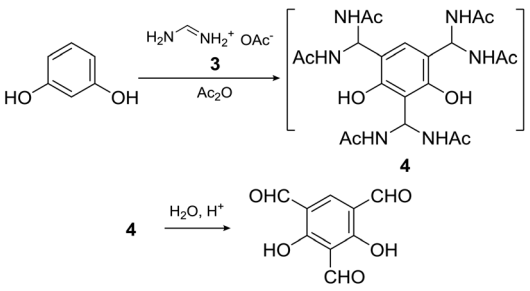
oxidized to iminiums through hydride transfer under the conditions of the reaction. Although this reaction is effective for many substrates, formation of polymeric side-products complicates its application to highly reactive substrates like phloroglucinol, **1**. Thus, state-of-the-art procedures to formylate **1** require a large excess of expensive CF_3CO_2H, and give a low yield of 15%.

In our recent work to find an improved preparation of 2,4,6-triformylphloroglucinol (TFP), a molecule that has proven useful for liquid crystals,[31] COFs,[32,33] and other materials,[34–39] we found that a method originally proposed for the formylation of anilines[40] can bring about efficient formylation of phenols, Scheme 2. This method uses acetic anhydride and formamidine acetate, **3**, which is commercially available and easily prepared from triethyl orthoformate.[41] We have since optimized the reaction conditions to effect the multiple formylation of a variety of phenols in high yield and under mild conditions.

Compared to the iminium substituents encountered in Vilsmeier intermediates, the $CH(NHAc)_2$ groups in intermediate **4** are less deactivating, explaining the improved access to compounds with multiple formyl groups using this method. Except for acetic acid, which is produced as a byproduct, strong acids and bases are avoided, allowing the use of sensitive substrates.

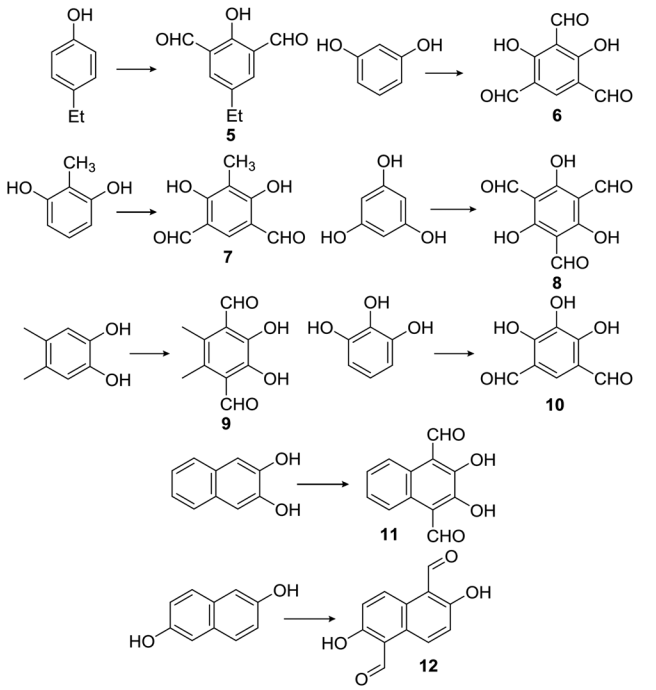
Table 1 describes the formylation of a number of phenol derivatives using the present method. In exploring the scope of this reaction, we used it in challenging aldehyde syntheses, some inspired by our previous experience with Schiff-base precursors. For instance, the state-of-the-art procedures for compounds **8** and **9** use the Duff reaction and give poor yields (22% and 10%, respectively).[42–44] Similarly, the preparation of **11** was previously accomplished in a four-step synthesis involving protection and deprotection of the OH groups.[45]

We attempted the formylation of 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene under similar conditions to those used for the preparation of **6** and **8** but found that these substrates were substantially less reactive. Thus, the presence of the hydroxyl group seems to be essential for facile formylation. Moreover, formylation occurred in the *ortho* position relative to the hydroxyls for all substrates—no *p*-formyl products were observed.



Scheme 2 Formylation of a phenol derivative using formamidine acetate and acetic anhydride.

Table 1 Formamidine acetate–acetic anhydride formylation of various phenols



Product	F.A.[a] equiv.	Ac_2O equiv.	Solvent	Temp.	Duration	Yield (%)
5	8	16	Dioxane[b]	100 °C	48 h	69
6	4	8	THF	85 °C[c]	24 h	82
7[d]	4	8	THF	55 °C	24 h	80
8	5	10	THF	45 °C	24 h	51
9	5	10	Dioxane[b]	95 °C	72 h	51
10	4	8	Dioxane[b]	95 °C	48 h	76
11	8	16	Dioxane[b]	95 °C	48 h	52
12	8	16	Dioxane[b]	95 °C	48 h	89

[a] Formamidine acetate. [b] 1,4-Dioxane. [c] Reaction carried out above boiling point pf solvent in a bomb. [d] Yield of **7** using the Duff procedure is 44%.[46]

In summary, formylation reactions using formamidine acetate and acetic anhydride address some of the main shortcomings of the Vilsmeier and Duff procedures. Namely, harsh conditions and deactivating iminium intermediates are avoided, enabling efficient multiple formylation without the complication of side reactions. The efficiency of the present route makes it the method of choice for the preparation of a wide variety of formylated phenols, as demonstrated with several interesting examples here. We anticipate that this method of formylation will be of considerable use for chemists.

We thank NSERC for funding this research (Discovery Grant).

Notes and references

1 J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemistry*, 2000.

2 K. P. C. Vollhardt and N. E. Schore, in *Organic Chemistry*, 2010, pp. 775–826.
3 S. Guieu, A. K. Crane and M. J. MacLachlan, *Chem. Commun.*, 2011, **47**, 1169–1171.
4 M. J. MacLachlan, *Pure Appl. Chem.*, 2006, **78**, 837–888.
5 P. D. Frischmann, J. Jiang, J. K.-H. Hui, J. J. Grzybowski and M. J. MacLachlan, *Org. Lett.*, 2008, **10**, 1255–1258.
6 S. Akine, T. Taniguchi and T. Nabeshima, *Tetrahedron Lett.*, 2001, **42**, 8861–8864.
7 H. L. C. Feltham, F. Klöwer, S. A. Cameron, D. S. Larsen, Y. Lan, M. Tropiano, S. Faulkner, A. K. Powell and S. Brooker, *Dalton Trans.*, 2011, **40**, 11425–11432.
8 S.-Y. Ding, J. Gao, Q. Wang, Y. Zhang, W.-G. Song, C.-Y. Su and W. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 19816–19822.
9 L. Xu, X. Zhou, Y. Yu, W. Q. Tian, J. Ma and S. Lei, *ACS Nano*, 2013, **7**, 8066–8073.
10 S.-Y. Ding and W. Wang, *Chem. Soc. Rev.*, 2013, **42**, 548–568.
11 H.-S. Xu, S.-Y. Ding, W.-K. An, H. Wu and W. Wang, *J. Am. Chem. Soc.*, 2016, **138**, 11489–11492.
12 Y. Peng, G. Xu, Z. Hu, Y. Cheng, C. Chi, D. Yuan, H. Cheng and D. Zhao, *ACS Appl. Mater. Interfaces*, 2016, **8**, 18505–18512.
13 H. Ma, B. Liu, B. Li, L. Zhang, Y.-G. Li, H.-Q. Tan, H.-Y. Zang and G. Zhu, *J. Am. Chem. Soc.*, 2016, **138**, 5897–5903.
14 C. R. DeBlase, K. Hernández-Burgos, K. E. Silberstein, G. G. Rodríguez-Calero, R. P. Bisbey, H. D. Abruña and W. R. Dichtel, *ACS Nano*, 2015, **9**, 3178–3183.
15 K. Reimer, *Ber. Dtsch. Chem. Ges.*, 1876, **9**, 423–424.
16 K. Reimer and F. Tiemann, *Ber. Dtsch. Chem. Ges.*, 1876, **9**, 824–828.
17 H. Wynberg, *Chem. Rev.*, 1960, **60**, 169–184.
18 G. Casnati, M. Crisafulli and A. Ricca, *Tetrahedron Lett.*, 1965, **6**, 243–245.
19 G. Casiraghi, G. Casnati, G. Puglia, G. Sartori and G. Terenghi, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1862.
20 N. U. Hofsløkken and L. Skattebøl, *Acta Chem. Scand.*, 1999, **53**, 258–262.
21 A. Vilsmeier and A. Haack, *Chem. Ber.*, 1927, **60**, 119.
22 E. Campaigne and W. L. Archer, *J. Am. Chem. Soc.*, 1953, **75**, 989–991.
23 T. Mallegol, S. Gmouh, M. A. Meziane, M. Blanchard-Desce and O. Mongin, *Synthesis*, 2005, 1771–1774.
24 R. Neidlein and R. Leidholdt, *Chem. Ber.*, 1986, **119**, 844–849.
25 N. Akhtar, M. A. Munawar and M. Siddiq, *Indian J. Chem.*, 1986, **25B**, 328–328.
26 E. Deiters, F. Gumy and J.-C. G. Bünzli, *Eur. J. Inorg. Chem.*, 2010, **2010**, 2723–2734.
27 J. C. Duff and E. J. Bills, *J. Chem. Soc.*, 1932, 1987–1988.
28 J. C. Duff, *J. Chem. Soc.*, 1941, 547–550.
29 J. C. Duff, *J. Chem. Soc.*, 1945, 276–277.
30 W. E. Smith, *J. Org. Chem.*, 1972, **37**, 3972–3973.
31 A. S. Achalkumar, U. S. Hiremath, D. S. S. Rao, S. K. Prasad and C. V. Yelamaggad, *J. Org. Chem.*, 2013, **78**, 527–544.
32 D. B. Shinde, H. B. Aiyappa, M. Bhadra, B. P. Biswal, P. Wadge, S. Kandambeth, B. Garai, T. Kundu, S. Kurungot and R. Banerjee, *J. Mater. Chem. A*, 2016, **4**, 2682–2690.
33 Y. Peng, Z. Hu, Y. Gao, D. Yuan, Z. Kang, Y. Qian, N. Yan and D. Zhao, *ChemSusChem*, 2015, **8**, 3348–3348.
34 S. H. M. Mehr, B. O. Patrick and M. J. MacLachlan, *Org. Lett.*, 2016, **18**, 1840–1843.
35 P. Kieryk, J. Janczak, J. Panek, M. Miklitz and J. Lisowski, *Org. Lett.*, 2016, **18**, 12–15.
36 J. S. Foster, J. M. Żurek, N. M. S. Almeida, W. E. Hendriksen, V. A. A. le Sage, V. Lakshminarayanan, A. L. Thompson, R. Banerjee, R. Eelkema, H. Mulvana, M. J. Paterson, J. H. van Esch and G. O. Lloyd, *J. Am. Chem. Soc.*, 2015, **137**, 14236–14239.
37 B. Feldscher, A. Stammler, H. Bögge and T. Glaser, *Polyhedron*, 2011, **30**, 3038–3047.
38 X. Jiang, Y.-K. Lim, B. J. Zhang, E. A. Opsitnick, M.-H. Baik and D. Lee, *J. Am. Chem. Soc.*, 2008, **130**, 16812–16822.
39 M. Sauer, C. Yeung, J. H. Chong, B. O. Patrick and M. J. MacLachlan, *J. Org. Chem.*, 2006, **71**, 775–788.
40 W. Petersen, *US Pat.*, 4394314, 1983.
41 E. C. Taylor, W. A. Erhart and M. Kawanisi, *Org. Synth.*, 1966, **46**, 39.
42 J. H. Chong, M. Sauer, B. O. Patrick and M. J. MacLachlan, *Org. Lett.*, 2003, **5**, 3823–3826.
43 K. E. Shopsowitz, D. Edwards, A. J. Gallant and M. J. MacLachlan, *Tetrahedron*, 2009, **65**, 8113–8119.
44 C. V. Yelamaggad, R. Prabhu, D. S. S. Rao and S. K. Prasad, *Tetrahedron Lett.*, 2010, **51**, 4579–4583.
45 A. J. Gallant, M. Yun, M. Sauer, C. S. Yeung and M. J. MacLachlan, *Org. Lett.*, 2005, **7**, 4827–4830.
46 K. Skonieczny, G. Charalambidis, M. Tasior, M. Krzeszewski, A. Kalkan-Burat, A. G. Coutsolelos and D. T. Gryko, *Synthesis*, 2012, **44**, 3683–3687.