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Neat Formic Acid: an Excellent N-Formylating Agent for Carbazoles, 3-Alkylindoles, Diphenylamine and Moderately Weak Nucleophilic Anilines

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NEAT FORMIC ACID : AN EXCELLENT *N*-FORMYLATING AGENT FOR CARBAZOLES, 3-ALKYLINDOLES, DIPHENYLAMINE AND MODERATELY WEAK NUCLEOPHILIC ANILINES

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Abstract : Neat formic acid alone efficiently *N*-formylates carbazoles, 3-alkylindoles, diphenylamine and even moderately weak nucleophilic anilines to furnish the corresponding *N*-formyl derivatives in 72-87% yields.

The development of procedures for the construction of the N-C bond is highly important. *N*-Formylation is an important step in organic synthesis. The reagents that are currently available for *N*-formylation are well documented.[1] The merits and demerits of the formylating agents developed thereafter and the consequent development of a stable *N*- and *O*-formylating agent, viz. *N*-formyl-

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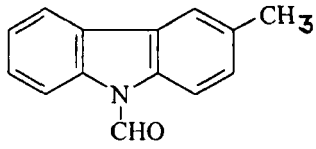
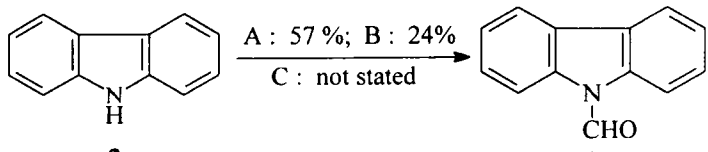
benzotriazole have very recently been reported.[2] During our work on the isolation and identification of a new metabolite, *N*-formyl-3-methylcarbazole (**1**), from the roots of the 'curry leaf plant', *Murraya koenigii*,[3] we wished to provide additional structural support for **1** by preparing it by the direct *N*-formylation of 3-methylcarbazole. The latter was also isolated by us from the same plant.[3] As a result of our efforts we discovered that efficient *N*-formylation of various carbazoles, 3-alkylindoles, diphenylamine and even moderately weak nucleophilic anilines can be accomplished by neat formic acid alone, which has been known to successfully *N*-formylate organometallic compounds.[1] Our findings have been briefly communicated herein.



1

For the *N*-formylation of 3-methylcarbazole, we intended to employ any one of the reagents that have been reported to successfully *N*-formylate carbazole (**2**) itself. Three such methods could be traced in the literature.[4-6] On inspection, however, each of these reagents appeared to offer only limited success. Thus, the classical Vilsmeier reaction ($POCl_3$, DMF) is reported to furnish *N*-formyl-carbazole (**3**) in only 57% yield,[4] whereas the treatment of carbazole with the ambident diethoxycarbenium tetrafluoroborate furnished the same product in a mere 24% yield.[5] The third and latest method involved the use of triethyl

orthoformate (as both solvent and electrophile) in the presence of *p*-toluenesulfonic acid as catalyst,[6] followed by hydrolysis of the resulting amide acetal by hydrochloric acid or by long contact with silica gel; here the yield of **3** was not stated (Scheme 1).



2 **3**

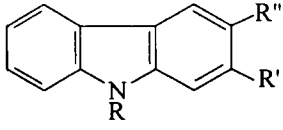
A : $POCl_3$, DMF; 45^0; 1.5 hr

B : $\overset{\oplus}{C}H(OEt)_2\overset{\ominus}{B}F_4$, $(MeOCH_2)_2$; 0^0; 4 hr → rt

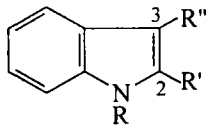
C : $HC(OEt)_3$; *p*-TsOH; 80^0; 48 hr; HCl or SiO_2

Scheme 1

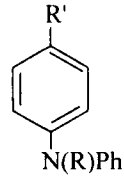
This situation called for the development of newer, more efficaceous *N*-formylating agents for carbazoles. We have discovered in this connection that



4, 5 : R' = Me; R" = H
6, 1 : R' = H; R" = Me
7 : R' = H; R" = NO_2



8, 9 : R' = R" = Me
10, 11 : R' = H; R" = Me
12 : R' = Me; R" = H
13 : R' = Me; R" = CHO
14 : R' = R" = H



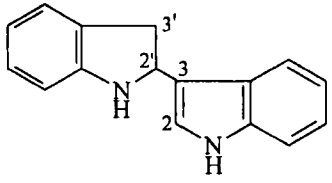
17 : R = R' = H
18 : R = CHO; R' = H
19 : R = H; R' = NO_2

For **4, 6, 7, 8, 10, 12, 13, 14 :** R = H; **1, 5, 9, 11 :** R = CHO

simple heating of **2** with neat formic acid (98%) at 100^0 for 3.5 hr furnished **3** in 86% yield. This success prompted us to utilise the reagent with other carbazoles

(**4, 6, 7**), indoles with (**8, 10**) and without (**12, 14**) substitution at C-3, diphenylamine (**17**) and its *p*-nitro derivative (**19**), acridone, imidazole and benzimidazole. The results, a mixed success, are presented in Table 1 and briefly discussed below. In the case of carbazole, facile *N*-formylation was the only course of the reaction. Expectedly, a methyl group (+I effect) at C-2 or C-3 of the carbazole nucleus required considerably less time for complete *N*-formylation, whereas a 3-nitro group (-I, -M effects) in the carbazole ring (**7**) completely retarded it.

With the indoles having a methyl group at C-3 (**8, 10**), exclusive *N*-formylation occurred with ease. With 2-methylindole (**12**), however, two products were obtained, none of which was the desired *N*-formyl derivative. The minor product (8%) was identified as the 3-formyl derivative **13**, but the major product (65%) could not be characterized. Curiously enough, indole itself (**14**) did not lead to any formylation and furnished, instead, the well-known 3,2'-dimer (**15**) and the 3, 3'-trimer (**16**), reported previously from the reaction of indole with acids under a variety of conditions.[10-12]



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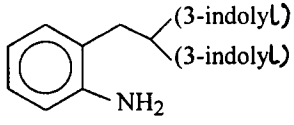


16

The reagent also worked well for **17**, furnishing its *N*-formyl derivative (**18**) with ease. But the reagent again proved ineffective in the case of *p*-nitrodiphenylamine (**19**), thus paralleling the case of 3-nitrocarbazole.

Table1. Results of *N*-formylation of carbazoles, indoles and diphenylamines*

Sl. no.	Substrate	Product	Reaction time (hr)	Yield (%)	M. p. (°C)	Reported m.p. (°C)	Ref.
1	**2**	**3**	3.5	86	94-96	94	5
2	**4**	**5**	0.5	87	oil	oil	5
3	**6**	**1**	0.5	82	58-60	58-60	3
4	**7**	-	5				
5	**8**	**9**	5	75	88	87-88	7
6	**10**	**11**	0.75	75	oil	oil	7
7	**12**[#]	**13**	15	8	201-202	200-201 198-200	8 9
8	**14**[Ψ]	**15** **16**	1	32 30	oil 88-90	- 173-177	10, 11 12
9	**17**	**18**	1	73	72-73	73-74	13a
10	**19**	-	4				

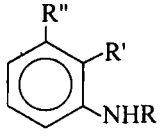
*Unless otherwise stated, the reactions were carried out by heating at 100°C. The reagent failed in the case of the nitro derivatives **7** and **19**. [#]The reaction was carried out at room temp., but the major product (65%), m.p. 192-194°, could not be characterized. [Ψ] The reaction was carried out at 15-20°.

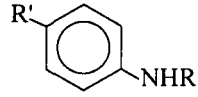
Acridone and benzimidazole failed to react even after prolonged hours of heating. The occurrence of acridone as 9-hydroxy acridine is probably the reason for its failure. Imidazole underwent complete conversion (TLC) in seven hours, but attempts to isolate the product resulted in the recovery of imidazole itself. This suggests that *N*-formylimidazole may have initially been formed but underwent hydrolysis during the aqueous work-up. This observation is in keeping with the fact that *N*-acyl imidazoles undergo extremely facile hydrolysis, e.g. even by moist air.[14]

Pertinently, the *N*-formylation of weakly nucleophilic anilines, such as 2-nitroaniline, can be achieved only under limited conditions.[15-18] This has led to the recent development of three more reagents for this purpose. The first one, cyanomethyl formate,[19] is difficult to prepare and requires the use of imidazole as catalyst in the cases of 3- and 4-nitroanilines. Conceivably, *in situ* generated *N*-formylimidazole (NFI)[20] was the actual *N*-formylating agent. The second reagent, *N*-formylbenzotriazole (NFB),[2] applied with success to 2- and 4-nitro-anilines, has, in turn, to be prepared from benzotriazole and formic acid in presence of the dehydrating agent, dicyclohexylcarbodiimide. Though superior to NFI, NFB required long time, e.g. 48 hrs for the very weakly nucleophilic 2-nitro-aniline. In the third method,[21] a mixture of formic acid and 4-trifluoromethyl-benzoic anhydride (TMBA) in presence of catalytic amount (10 mol%) of active titanium(IV) salt or ytterbium triflate in hexamethyldisilazane was used. The reagents and solvents are obviously expensive and the reaction conditions are

elaborate, although the yields were reportedly very good (>90%). Clearly, in analogy with the *in situ* formation of acetic formic anhydride (AFA) from a mixture of formic acid and acetic anhydride,[15] formic acid and TMBA are expected to form the mixed anhydride, formic 4-trifluoromethylbenzoic anhydride, probably the actual *N*-formylating agent. A rapid, mild and acid-free procedure has very recently been reported for the *in situ* preparation of formyl chloride which has been utilized for the *N*-formylation of various aryl amines.[22]

We reasoned that the aforesaid reagents and conditions used were unnecessarily complex, and we wondered if formic acid alone could accomplish this task. Accordingly, a number of anilines bearing substituents with varying degrees of electron-withdrawing properties were separately heated with formic





20, 21 : R' = NO_2 ; R" = H
22, 23 : R' = H; R" = NO_2
26, 27 : R' = COOH ; R" = H

24, 25 : R' = NO_2
28, 29 : R' = COOH
30, 31 : R' = Cl

For **20, 22, 24, 26, 28, 30** : R = H
For **21, 23, 25, 27, 29, 31** : R = CHO

acid at 100°. 2-, 3- and 4-Nitroanilines (**20, 22, 24**), and 2- and 4-aminobenzoic acids (**26, 28**) and 4-chloroaniline (**30**) were the substrates (Table 2).

As anticipated, all but 2-nitroaniline (**20**) underwent smooth *N*-formylation in *ca.* 80% yields in just 3-5 hours. For **20**, a mixture of formic acid and acetic

Table 2. Results of *N*-formylation of weakly nucleophilic anilines by heating with 98% formic acid at 100°C

Sl. no.	Substrate	Reaction time; Yield	M. p. (°C)	Lit. m. p. (°C)	Ref.
1	**20***	3 hr; 77%	122-124	122	13b
2	**22**	3 hr; 72%	135	134	13c
3	**24**	4 hr; 84%	198	194-195	13d
4	**26**	5 hr; 78%	162-163	169	13e
5	**28**	4.5 hr; 77%	266-268	268	13f
6	**30**	5 hr; 82%	100	102	13g

*Formic acid alone failed in this case. The substrate was heated with a mixture of HCO_2H and Ac_2O (2:1; v/v) at 100°C.

anhydride (2:1), i.e. *in situ* generated AFA was employed, since AFA is a well documented *N*-formylating agent for primary amines.[15] It brought about the desired *N*-formylation in only 3 hours, in sharp contrast to 20 hours required by the formic acid-TMBA-Ti/Yb-salt method[21] and 48 hours required by NFB.[2]

The superiority of neat formic acid over the extant *N*-formylating agents becomes obvious when the result of *N*-formylation of, for example, even

Table 3. Results of *N*-formylation of 4-nitroaniline (24)

Ref.	Reagent & conditions	Reaction time	Yield of **25**
19	HCO_2CH_2CN (1 eq.), imidazole (10 mol%), CH_2Cl_2, 75°	18 hr	60 %
2	N-formylbenzotriazole (1 eq.), THF, 67°	8 hr	82 %
Our work	HCO_2H (98%)	4 hr	84 %

themoderately weak nucleophilic amine 4-nitroaniline with formic acid is compared with those using two of the three recently developed reagents (Table 3).

Our work demonstrates that 98% formic acid is an efficient *N*-formylating agent for carbazoles, 3-alkylindoles, diphenylamine and even moderately weak nucleophilic anilines. The reagent is inexpensive and easily available, the reaction procedure and work-up are very simple and the yields of the *N*-formyl derivatives are quite high. The reagent is, therefore, expected to be widely used in future.

In many of the cases examined, even for moderately weak nucleophilic anilines, it is likely that 85% formic acid may also prove to be good enough for *N*-formylation. This was, however, not tested by us. Also, the applicability of neat formic acid in the case of complex amines bearing acid-sensitive groups remains to be demonstrated.

In conclusion, our results are in complete agreement with the remarks,

"The most attractive formylating agents are those readily obtained or inexpensive and commercially available", made in a previous review on formylating agents.[1]

EXPERIMENTAL

M.p.s (uncorrected) were determined on a Toshniwal apparatus. FT-IR spectra (KBr) were recorded on Perkin-Elmer 1600 and Nicolet Impact 410 spectrophotometers, the mass spectra on JEOL JMX-DX 300 (HRMS) and Shimadzu QP 1000 (LRMS) mass spectrometers and the ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR on Varian XL-400 and Bruker 300 DXP spectrometers, respectively. Column chromatographies (CC) were performed on silica gel (60-120 mesh; Qualigens, India) and TLC, both analytical and preparative, on silica gel G (E. Merck, India) plates. Some of the amines were procured from commercial sources and the rest were obtained as gifts. All new compounds were characterised by elemental analyses and/or HR-FABMS, IR, ^{1}H and sometimes ^{13}C NMR data. All the known compounds were identified by comparing their m.p.s with the reported ones and by ^{1}H NMR spectral analyses. Petrol refers to petroleum ether, b.p. $60\text{-}80^{0}$.

Formylation. General procedure. The amine (1 mM) was treated with 98% formic acid (2 ml) and, unless otherwise stated, was heated at 100°C till the amine was consumed (TLC). The solution was then poured into crushed ice, basified with solid $NaHCO_3$ and extracted with EtOAc (3x). The residue obtained

from the washed and dried (Na_2SO_4) EtOAc extract was either directly crystallised (entry 1, Table 1; all entries of Table 2) or purified by CC or PTLC (the rest).

Products from 2-methylindole. From 0.9 mM (118 mg) of **12** was obtained 110 mg of a solid mixture of two components (TLC). These were separated by PTLC in petrol-EtOAc (2:3) to furnish a major product (93 mg; Rf 0.28), m.p. 192-194° which could not be characterised and a minor product (11 mg; Rf 0.80) as a cream coloured solid, m.p. 201-202°, identified as **13** (Lit.[8,9] m.p. 200-201[0]; 198-200[0]) : IR (Thin film) : 3340 (NH), 1640 (ArCHO) cm^{-1}; HRMS *m/z* : 159.0678 $[M]^+$; calcd. for $C_{10}H_9NO$: 159.0684 $[M]^+$; ^1H NMR ($CDCl_3$) : δ 10.19 (1H, s, CHO), 8.71 (1H, br s, NH), 8.24 and 7.34 (1H, dd each, *J* 7.5, 2 Hz, H-4, 7), 7.27 and 7.24 (1H, dt each, *J* 2, 7.5 Hz, H-5,6), 2.74 (3H, s, 2-CH_3); ^{13}C NMR : δ 184.5 (d, CHO); 146.5, 134.9, 126.0 , 114.8 (all s, Ar-C), 123.4, 122.7, 120.8, 110.6 (all d, Ar-CH), 12.2 (q, CH_3).

Products from indole. From 50 mg of **14** was obtained a solid mixture (50 mg) of two components (TLC) which were separated by PTLC in C_6H_6-EtOAc (10:1) to furnish the dimer **15** as a colourless oil (16 mg; Rf 0.37) and the trimer **16** as a colourless powder (15 mg; Rf 0.18), m.p. 88-90°. These were fully identified by analysing their FAB-HRMS, ^1H and ^{13}C NMR, HMQC, HMBC and ^1H-^1H COSY spectra and comparing the data with the ^1H and ^{13}C NMR assignments reported earlier for the dimer[11] and the trimer.[11,12]

Acetylation of **16**. A solution of **16** (5 mg) in pyridine (0.2 ml) and Ac_2O (0.1 ml) was stirred for 3 hr, then concentrated in vacuo and the residue was purified by PTLC in hexane-EtOAc (1:1) to afford a colourless powder (3 mg), m.p. 190-192^0; FAB-HRMS (*m*-NBA) *m/z* : 416.1733 $[M+Na]^{+\cdot}$; calcd. for $C_{26}H_{25}N_3ONa$: 416.1739 $[M+Na]^+$. It was identified by its ^1H NMR (C_5D_5N) data (δ 1.87, 3H, s, *N*-Ac) and by comparing the m.p., 207-209^0, of this sample recrystallized from ethanol with that, 209-212^0, reported for it in the literature.[12]

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