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TECHNICAL NOTE

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Fast, Economic, and Green Synthesis of *N*-Formylated Benzotriazoles

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Supporting Information

ABSTRACT: Formylation is an integral part of organic, medicinal, and biological chemistry both in industrial and academic set-ups. A reflection of this importance is the number of approaches and reagents that have been developed to achieve it. We have developed a fast, efficient, and environmentally friendly procedure for the synthesis of *N*-formylated benzotriazoles.

INTRODUCTION

Formylation is an integral part of organic, medicinal, and biological chemistry both in industrial and academic setups. A reflection of this importance is the number of approaches and reagents that have been developed to achieve it.[1]

Most of the formylating reagents developed to date suffer from a number of severe disadvantages which have drastically curtailed their use. The most common formylating agents, ie. formic halides and formic anhydrides tend to suffer from stability problems and degrade easily upon storage. Cyanomethyl formate is a very useful, but difficult to prepare, formylating agent.[2] Isopropenyl formate is also a very fast and efficient reagent, but its synthesis requires a multistep sequence.[3] Coupling agents have also been used in conjunction with formic acid to achieve *N*- and *O*-formylation; however, the removal of the coupling agents' side products is often labour intensive.[4]

Katrizky developed *N*-formylbenzotriazole **1** as a stable and convenient alternative to achieve *N*- and *O*-formylation quickly and efficiently (Figure 1).[5] *N*-Formylbenzotriazole has become, in a large number of cases, the reagent of choice to achieve the mild and selective formylation of alcohols, amines, and even amides.[6]

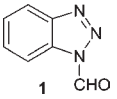

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Figure 1. *N*-Formylbenzotriazole.

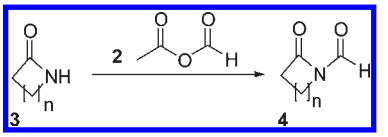
Katrizky's synthesis of *N*-formylbenzotriazole starts with benzotriazole which is coupled with formic acid in the presence of *N,N′*-dicyclohexylcarbodiimide (DCC) in anhydrous dichloromethane.[5] Unfortunately, while the coupling proceeds quickly and efficiently, the separation of the desired *N*-formylbenzotriazole from the urea side product is non-trivial and requires repeated and lengthy purification by recrystallisation which severely decreases the reaction's yield. Furthermore, even after repeated recrystallisation and trituration, the *N*-formylbenzotriazole obtained is often contaminated with urea byproducts making the yields highly variable and irreproducible. Efforts in our group to reduce the amount of urea side products by switching to *N,N′*-diisopropylcarbodiimide (DIC) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCi) have been unsuccessful at yielding pure *N*-formylbenzotriazole in significant amounts.

We now report a fast, efficient and environmentally friendly method for the synthesis of *N*-formylbenzotriazole, and substituted *N*-formylbenzotriazoles.

RESULTS AND DISCUSSION

We have previously demonstrated the use of acetic formic anhydride **2** for the efficient formylation of lactams **3** to generate the corresponding imides **4** (Scheme 1).[7] Unfortunately, acetic formic anhydride was not successful at formylating noncyclic amides, either under normal or refluxing conditions, most likely due to the lower nucleophilicity of the acyclic amides compared to the lactams.[8]

Scheme 1



However, it was hypothesized that acetic formic anhydride **2** might be effective at formylating benzotriazole **5** under mild conditions, and without the need for coupling agents and/or reaction additives. Thus, acetic formic anhydride was formed efficiently from acetic anhydride and formic acid, under either normal heating at 55 °C or at 80 °C under microwave conditions. The newly formed mixed anhydride was then treated with neat benzotriazole **5**, and the reaction was heated at 55 °C until completion by TLC. In our initial studies, the reaction mixture was dissolved in ethyl acetate, and the organic layer washed with water. Removal of the solvent under reduced pressure gave a white solid in 60% yield which consisted of *N*-formylbenzotriazole **1** and *N*-acetylbenzotriazole **6** in a 6:1 ratio, but most importantly, without any other side products (Scheme 2).

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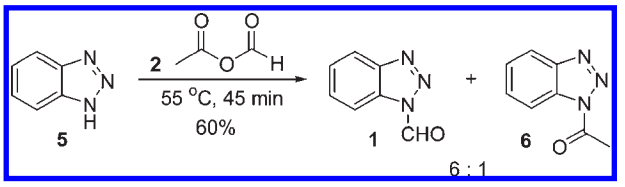
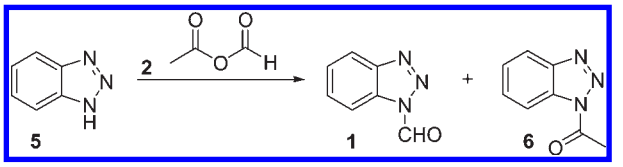
Scheme 2



Lowering the temperature of formylation to 0 °C shifted the ratio to 44:1 in favor of the formylated adduct **1**. Adding benzotriazole as a THF solution and further lowering the addition and reaction temperature to −10 °C resulted in increased selectivity to afford *N*-formylbenzotriazole in a 160:1 ratio and with no other side products. The lower reaction temperatures favor the preferential benzotriazole attack on the formyl as opposed to the more hindered acetyl carbonyl unit (both in the mixed anhydride and in the acetic anhydride present). This results in the selective ejection of acetate over a formate leaving group. Furthermore, the yield was significantly improved (94%) by eliminating the workup procedure and simply removing the acetic acid byproduct and THF under reduced pressure (Table 1).

Table 1



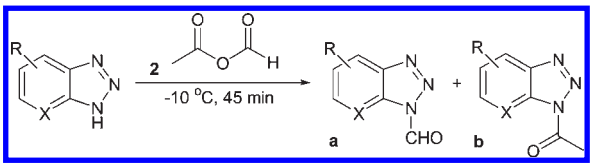
conditions	yield (%)	ratio (**1**:**6**)
55 °C, 45 min[a]	60[c]	6:1
0 °C, 45 min[a]	77[c]	44:1
−10 °C, 45 min[b]	94	160:1

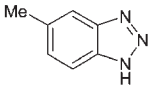
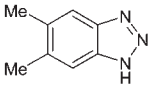
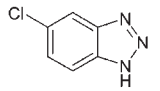
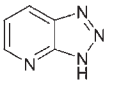
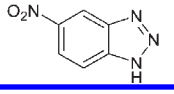
[a] Benzotriazole was added neat. [b] Benzotriazole was added as a 1 M solution in THF. [c] Water was added as part of the workup procedure.

The mixed anhydride formylation conditions were also applied successfully to differently substituted benzotriazoles in excellent yield. As expected, formylation of unsymmetrical, 5-substituted benzotriazoles results in various ratios of formylated regioisomers, depending on the electronic nature of the substituent group (Table 2). The presence of electron-withdrawing substituents on the benzotriazole unit resulted in a decrease in the formylation selectivity, presumably due to the lower reactivity of the benzotriazole core unit.

Acetic formic anhydride also formylated effectively the azo-analogue **13** (entry 4) in excellent yield, and with good selectivity relative to the acetylated product. Interestingly, a 12:1 ratio of *N*-formylated regioisomers was obtained (Scheme 3). NOE studies show that formylation takes place preferentially on the same side as the benzene ring's nitrogen. This regioselectivity could potentially be explained through a zwitterionic intermediate analogous to that proposed by Carpino for 1-hydroxy-7-azabenzotriazole (HOAt).[9]

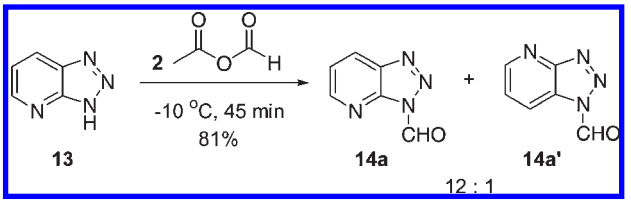
Table 2



Entry	Substrate		Yield	Ratio	
1		**7**	99%	43 : 1	**8a**[i] : **8b**
2		**9**	94%	193.6 : 1	**10a** : **10b**
3		**11**	99%	23 : 1	**12a**[ii] : **12b**
4		**13**	96%	5.4 : 1	**14a**[iii] : **14b**
5		**15**	90%	4.5 : 1	**16a**[iv] : **16b**

[i] Obtained as a 1.6:1.0 mixture of regioisomers. [ii] Obtained as a 2.5:1.0 mixture of regioisomers. [iii] Obtained as a 12.0:1.0 mixture of regioisomers. [iv] Obtained as a 5.7: 1.0 mixture of regioisomers.

Scheme 3



Having explored the scope of the reaction conditions to formylate other benzotriazole systems, the feasibility for scaling up the process was then assessed (Table 3). We are pleased to see that increasing the scale of the reaction had minimal effect on the yield and the purity of the *N*-formylbenzotriazole **5** obtained. Most importantly, there was no product purification required regardless of the reaction scale.

Furthermore, the amount of THF used can be decreased by increasing the concentration of benzotriazole in THF up to 1.8 M without any significant drop in yield, purity, or selectivity. Preliminary results suggest that it might be possible to use non-anhydrous conditions during the formylation step. Efforts arecurrently underway to determine the maximum permissible water levels.

In conclusion, we have developed a fast, efficient, and environmentally friendly procedure for the synthesis of *N*-formylated benzotriazoles. This method requires minimal amounts of organic solvents, produces acetic acid as the only significant side product, and requires no purification. The THF used in the reaction mixture can be recovered during the evaporation

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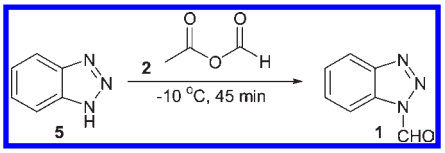
Table 3



entry	amount (g)	yield (%)	purity (%)
1	2.98[a]	94	99+
2	4.16[a]	96	98.5
3	13.09[a]	98	99+
4	29.00[b]	99	99+
5	64.29[b]	98.5	98.5

[a] Added as a 1 M soln in THF. [b] Added as a 1.8 M soln in THF.

step, thus causing minimal environmental impact and reducing production costs.

As a whole, this procedure is a great improvement compared to other methods available currently for its synthesis both in terms of cost, yield, and overall efficiency. We are in the process of applying this straightforward methodology for the development of asymmetric and tunable formylating agents based on the benzotriazole framework.

EXPERIMENTAL SECTION

All reactions were performed under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF) was purified through a solvent purification system. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C.

IR spectra were recorded as thin films using a Fourier transform spectrometer equipped with a golden gate. Only diagnostic absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}).

Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded at 400 MHz and 100 MHz or at 500 and 125 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dm = double multiplet), and (3) coupling constant (J) quoted in Hertz to the nearest 0.1 Hz.

High-resolution mass spectra were recorded by electrospray and chemical ionisation at a resolution of 15000 full widths at half height.

TLC was performed on aluminium sheets precoated with silica (Merck silica gel 60 F_{254}). The plates were visualised by the quenching of UV fluorescence ($\lambda_{max\ 254\ nm}$).

Representative Procedure. Commercial grade acetic anhydride (1 equiv) is treated with 100% formic acid (2 equiv), and the resulting mixture is stirred under argon either at 55 °C for 3 h for conventional heating or at 80 °C for 45 min for microwave heating. The resulting crude anhydride mixture is then analysed by ^{1}H NMR and the yield of mixed anhydride determined (42−58%).

The mixed anhydride is then cooled down room to temperature and added slowly to a −10 °C solution of the desired benzotriazole in THF (0.9 equiv based on the amount of anhydride present as determined from the ^{1}H NMR). The reaction is then stirred at −10 °C until complete as indicated by TLC analysis (45 min on a 540 mmol scale). The solvent and acetic acid byproducts are then removed under reduced pressure to yield the desired *N*-formylbenzotriazole without the need of purification.

N-Formylbenzotriazole, ***1***. In the largest scale reaction performed to date, 75.6 mL (800 mmol) of acetic anhydride was treated with 100% formic acid (60.3 mL, 1.6 mol), and the resulting mixture was stirred at 55 °C under conventional heating for 3 h. The mixed anhydride was cooled down to room temperature and added slowly to a −10 °C solution of benzotriazole (64.29 g, 540 mmol, 0.9 equiv based on the amount of anhydride present as determined from the ^{1}H NMR) in THF (300 mL). The resulting mixture was then stirred at −10 °C until complete as indicated by TLC analysis (45 min.). The solvent was then removed under vacuum to yield 78.8 g (98.5%) of the desired *N*-formylbenzotriazole as a white solid without the need of purification (98.5% purity as determined by ^{1}H NMR). The physical data obtained for *N*-formylbenzotriazole **1** is in accordance with that reported in the literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.86 (1H, s), 8.26 (1H, d, J = 8.0 Hz), 8.18 (1H, dt, J = 8.0, 1.0 Hz), 7.71 (1H, ddd, J = 8.2, 7.2, 1.0 Hz), 7.59 (1H, ddd, J = 8.2, 7.2, 1.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7, 146.5, 130.7, 129.8, 127.0, 120.4, 113.6.

IR ν_{max}(film)/cm^{-1} 3105, 1723, 1604, 1595.

HRMS calcd for $C_7H_5ON_3$: 147.0433. Found 147.0435.

5-Methyl N-formylbenzotriazole, ***8a*** *and 6-Methyl-N-formylbenzotriazole,* ***8a′***. The methyl-substituted *N*-formylbenzotriazoles **8a** and **8a′** were obtained as a 1.6:1.0 mixture of regioisomers (**8a:8a′**).

υ_{max} (neat)/cm^{-1}; 2959, 2924, 1699, 1617, 1491, 1440, 1372, 1349, 1300, 1062.

HRMS (ESI) found 161.0592, $C_8H_7ON_3$ calculated 161.0589.

8a: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.82 (1H, s), 8.04 (1H, s), 7.99 (1H, ddd, J = 8.5, 1.4, 0.5 Hz), 7.38 (1H, dd, J = 8.4, 1.1 Hz), 2.58 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.9, 145.1, 142.0, 130.3, 128.9, 119.7, 113.1, 22.1.

8a′: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.83 (1H, s), 8.10 (1H, ddd, J = 8.4, 1.0, 0.4 Hz), 7.91 (1H, s), 7.52 (1H, dd, J = 8.3, 1.0 Hz), 2.56 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7, 147.1, 137.4, 132.5, 128.2, 119.5, 112.9, 21.6.

5,6-Dimethyl N-formylbenzotriazole, ***10a***. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.80 (1H, s), 8.01 (1H, s), 7.88 (1H, s), 2.47 (3H, s), 2.45 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 145.6, 141.4, 136.9, 128.7, 119.6, 113.2, 20.9, 20.5.

υ_{max} (neat)/cm^{-1}; 3294, 2946, 2918, 2358, 1727, 1714, 1587, 1478, 1463, 1448, 1203, 1060. HRMS (ESI) found 175.0747 calculated for $C_9H_9ON_3$ 175.0746.

5-Chloro N-formylbenzotriazole, ***12a*** *and 6-Chloro-N-formylbenzotriazole,* ***12a′***. The chloro-substituted *N*-formylbenzotriazoles **12a** and **12a′** were obtained as a 2.5:1.0 mixture of regioisomers (**12a:12a′**).

υ_{max} (neat)/cm^{-1}; 3101, 3010, 2956, 2834, 1910, 1759, 1732, 1608, 1586, 1460, 1367, 1220. HRMS (ESI) found 181.0036 calculated for $C_7H_4ON_3Cl$ 181.0043.

12a. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.82 (1H, s), 8.28 (1H, dm, J = 1.8 Hz), 8.08 (1H, dd, J = 8.8, 0.5 Hz), 7.55 (1H, dd, J = 8.8, 1.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.5, 145.0, 137.5, 130.5, 128.1, 121.2, 113.7.

12a′. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.83 (1H, s), 8.20 (1H, dm, J = 8.7 Hz), 8.15 (1H, dd, J = 1.8, 0.6 Hz), 7.68 (1H, dd,

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J = 8.6, 1.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 143.5, 132.8, 128.6, 131.5, 120.0, 114.3.

N-Formyl-4-azabenzotriazole, ***14a*** *and N-Formyl-7-aza-benzotriazole,* ***14a′***. The *N*-formyl-aza-benzotriazoles **14a** and **14a′** were obtained as a 12.0:1.0 mixture of regioisomers (**14a:14a′**).

υ_{max} (neat)/cm^{-1}; 2680, 1728, 1594, 1584, 1399, 1376, 1259, 1060.

HRMS (CI) found 149.0472 calculated for $C_6H_5ON_4$ 149.0463.

14a. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.03 (1H, s), 8.91 (1H, dd, J = 4.5, 1.5 Hz); 8.65 (1H, dd, J = 8.2, 1.4 Hz), 7.86 (1H, dd, J = 8.3, 4.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.1, 163.1, 149.7, 144.8, 125.4, 123.3.

14a′. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.98 (1H, s), 8.87 (1H, dd, J = 4.4, 1.6 Hz), 8.64 (1H, dd, J = 8.3, 1.5 Hz), 7.81 (1H, dd, J = 8.3, 4.5 Hz).

5-Nitro N-formylbenzotriazole, ***16a*** *and 6-Nitro-N-formyl-benzotriazole,* ***16a′***. The nitro-substituted *N*-formylbenzotriazoles **16a** and **16a′** were obtained as a 5.7:1.0 mixture of regioisomers (**16a:16a′**).

υ_{max} (neat)/cm^{-1}; 3173, 3098, 1750, 1742, 1618, 1520, 1338, 1204.

HRMS (ESI) found 192.0284 calculated for $C_7H_4O_3N_4$ 192.0283.

16a. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.90 (1H, s), 9.09 (1H, d, J = 1.7 Hz), 8.64 (1H, dd, J = 9.0, 2.0 Hz), 8.42 (1H, d, J = 8.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 146.0, 132.8, 125.7, 117.2, 116.9, 114.2.

16a′. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.91 (1H, s), 9.05 (1H, d, J = 1.8 Hz), 8.56 (1H, dd, J = 9.0, 2.0 Hz), 8.45 (1H, d, J = 9.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.0, 146.5, 125.3, 122.1, 121.4, 117.2, 110.3.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterisation data of the described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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