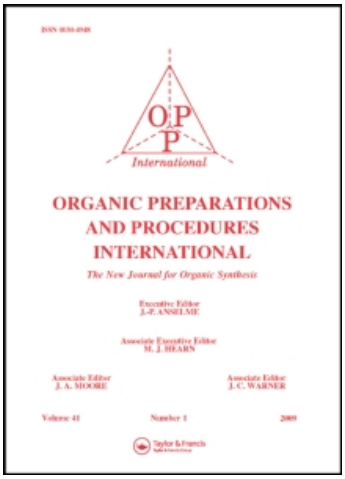


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PERFORMANCE FLUIDS AS AN INERT MEDIUM FOR THE PREPARATION OF BENZOTRIAZOLE DERIVATIVES

Alan R. Katritzky[a]; Dorin Toader[a]; Jinlong Jiang[a]
[a] Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL

To cite this Article Katritzky, Alan R. , Toader, Dorin and Jiang, Jinlong(1995) 'PERFORMANCE FLUIDS AS AN INERT MEDIUM FOR THE PREPARATION OF BENZOTRIAZOLE DERIVATIVES', Organic Preparations and Procedures International, 27: 2, 179 — 184
To link to this Article: DOI: 10.1080/00304949509458452
URL: http://dx.doi.org/10.1080/00304949509458452

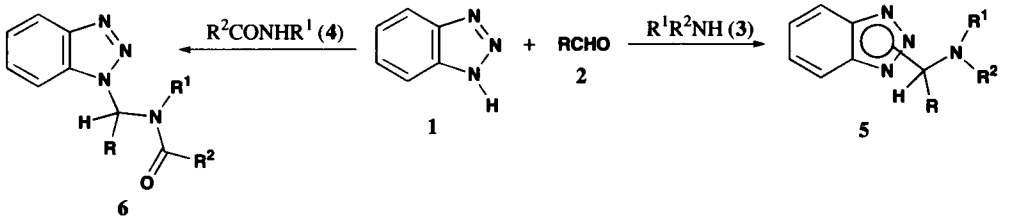
ORGANIC PREPARATIONS AND PROCEDURES INT., 27 (2), 179-184 (1995)

PERFORMANCE FLUIDS AS AN INERT MEDIUM FOR THE PREPARATION OF BENZOTRIAZOLE DERIVATIVES

Alan R. Katritzky*, Dorin Toader and Jinlong Jiang

Center for Heterocyclic Compounds, Department of Chemistry
University of Florida, Gainesville, FL 32611-7200

Organic reactions can be carried out either in the presence or absence of a solvent. An important reason for using a solvent is to limit the reaction temperature to its boiling point. If reactions are heated without a solvent for a prolonged period, two problems often arise: (*i*) the reaction components are more easily oxidized in the absence of the protection provided by the solvent vapor; (*ii*) the desired constant reaction temperature is sometimes difficult to maintain. Recently, Zhu reported the use of perfluorocarbon (PFC) fluids (performance fluids) as the inert medium for ester transformations as well as for acetal, ketal and enamine syntheses.[1] Performance fluids provide a novel medium in which the substrates react as though in the absence of solvent, but the reaction proceeds as though in the presence of solvent with respect to maintenance of temperature and protection by the solvent vapor. We now report that some benzotriazole derivatives are conveniently prepared in performance fluids. Recent publications from our laboratory have demonstrated the synthetic utility of benzotriazole products of types **5** and **6** as intermediates for the preparation of amines and amides.[2] Their preparation from aldehydes, benzotriazole and amines or amides is usually carried out in benzene or toluene by the Dean-Stark method.[3-5] Although many of these preparations gave good results, several



limitations such as occasional low yields, and the long reaction times (up to 72 hrs) required for preparation of amide derivatives **6** by the normal Dean-Stark method[4] were evident. We now describe an improved and more powerful method of water-removal using performance fluids as an inert medium in conjunction with a reversed Dean-Stark trap.

TABLE 1. Preparative Data of Benzotriazole Derivatives **5** and **6**

	Product								Literature		
Cmpd	R	R^1	R^2	PF	Time (hrs)	Yield (%)	mp (°C)	Method	Time (hrs)	mp (°C)	Yield (%)
5a	Ph	H	pyridin-2-yl	5070	3	98		A[a]	4	148-150	75
5b	*i*-Pr	H	4-$CH_3C_6H_4$	5070	3	95					
6a	4-$O_2NC_6H_4$	H	Ph	5080	6	97	225-227	C[b]	24	219-221	81
6b	H	H	4-$CH_3C_6H_4$	5070	2	95	176-177	D[a]	32	181-182	32
6c	H	H	NH_2	5080	2	97	187-189				
6d	Ph	-$(CH_2)_3$-		5070	3	95	94-96				
6e	*i*-Pr	-$(CH_2)_3$-		5080	4	92	133-135				
6f	H	-$(CH_2)_3$-		5070	2	95	82-83	B[c]	24	78-80	96
6g	Ph	-$(CH_2)_4$-		5080	4	52[d]					
6h	*i*-Pr	-$(CH_2)_4$-		5080	5	77[d]	111-112				
6i	*i*-Pr	-$(CH_2)_5$-		5080	5	44[d]	113-114				
6j	H	Me	Ph	5080	2	80	98-99	C[c]	48	111-112	80

a) Unpublished work in our group. b) ref. 6. c) ref. 4. d) Yields after recrystallization. Methods: A = Dean-Stark with benzene; B = reflux in AcOH; C = Dean-Stark with toluene and TsOH as catalyst, D = benzotriazole, paraformaldehyde and *p*-toluonitrile.

Performance fluids belong to classes of perfluorinated and saturated aliphatic compounds such as perfluoroalkanes or perfluoroalkyl ethers. They have a high density and are immiscible with water and organic compounds.[1] Our reactions were carried out in either PFC 5070 (bp 82°) or PFC 5080 (bp 104°). In general, the starting materials were mixed and heated under reflux with a reversed Dean-Stark trap. The denser phase, PFC, returned to the reaction mixture and water remained in the trap. The reactants, including benzotriazole, were usually molten during refluxing. Two phases, the organic mixture and performance fluid, were present throughout the duration of the reaction. All reactions were monitored by the quantity of water distilled. Upon completion of the reaction, solid products were obtained by simple filtration. The performance fluid was washed with ethanol to remove contaminants before reuse.

When benzotriazole, aldehyde and primary or secondary aromatic amine were refluxed in performance fluid under reversed Dean-Stark conditions, benzotriazole derivatives **5** were obtained quantitatively as a mixture of the 1- and 2-benzotriazolyl isomers, with the 2-benzotriazolyl isomer predominating. When volatile isobutyralde was used (for the preparation of **5b**), the reaction did not occur instantaneously. Refluxing for 1-2 hrs was required to establish equilibrium before the reversed Dean-Stark trap was attached. When this initial reflux was not performed, some of the unreacted isobutyraldehyde was removed leading to an incomplete reaction. An alternative was to use an excess of the volatile isobutyraldehyde to convert the less volatile benzotriazole and *p*-methylaniline into the product **5b**.

TABLE 2. ^{13}C NMR Spectral Data of Compounds **5** and **6** (δ, ppm)

Cmpd	Benzotriazole						C=O	NCH_2Bt or NCHBt	R	R^1	R^2
	C4	C5	C6	C7	C7a	C3a					
5a[a]	119.9 119.6	124.0 129.0	129.5 129.0	110.6 119.6	131.9 146.2	147.9 146.2	–	69.1	126.4, 128.9 131.9, 137.0	–	155.8, 148.8, 148.2 137.3, 137.9
5b[a]	120.1 118.2	126.1 129.7	127.6 129.7	110.2 118.2	129.8 142.5	143.7 142.5	-	81.65 76.57	19.1, 19.4, 35.1, 18.5, 18.7, 34.5	–	20.2, 19.4
6a[b]	119.9	124.1	128.3	111.5	132.6	145.7	167.4	65.6	148.2, 145.8, 143.7, 133.2	–	132.7, 128.4, 122.2, 128.8
6b	119.2	124.3	129.2	111.2	132.5	145.9	167.7	51.5	-	-	21.4, 127.4, 127.9, 129.9, 142.9
6c[b]	118.9	124.0	127.2	111.4	132.0	145.3	156.7	52.6	-	-	-
6d	119.4	124.5	128.9	110.8	132.6	144.8	175.3	65.8	127.0, 127.9, 128.9, 134.1		17.7, 30.1, 44.1
6e	119.1	123.9	127.4	109.8	132.9	144.9	175.2	68.3	18.6, 18.3, 28.2		28.2, 30.3, 42.0
6f	119.2	124.1	127.7	110.2	131.8	145.7	175.3	53.4	-		45.6, 30.1, 17.2
6g[a]	119.6 118.4	124.2 133.9	127.7 133.9	110.1 118.4	133.4 143.9	145.1 143.9	171.0	66.2 74.2	133.9, 128.7, 128.6, 127.1		20.7, 22.8, 22.9, 32.2,.32.4, 44.1, 44.7
6h	119.3	124.2	127.7	110.5	133.4	145.3	170.7	69.3	27.6, 18.3, 19.0		32.1, 22.6, 27.6, 41.5
6i	119.5	124.3	127.7	110.4	133.3	145.3	176.5	70.3	28.4, 18.6, 19.0		29.41, 23.0, 28.4, 37.0, 42.8
6j	119.5	124.2	128.3	110.9	132.2	145.9	171.8	57.8	-	36.2	134.4, 130.3, 127.8, 126.9

a) Mixture of 1- and 2-benzotriazolyl derivatives. *b)* In DMSO-d_6.

Benzotriazole adducts **6** were synthesized similarly from 2-pyrrolidinone, benzotriazole and the appropriate aldehyde in excellent yields. 1-Hydroxymethyl-1*H*-benzotriazole, readily available from benzotriazole and aqueous formaldehyde solution,[7] was used in the preparation of adducts **6b, c, f, j**. Reactions of amides other than 2-pyrrolidinone were slower and a catalytic amount of an acidic resin was required. However, we found that benzamide, 4-methylbenzamide, urea and N-methylbenzamide gave the desired products **6a-c** and **6j** in excellent yields, without the need for further purification. The solid products were conveniently collected by simple filtration. Further purification was necessary when 2-piperidone and ε-caprolactam were reacted with the appropriate aldehyde to give adducts **6g-i.** The examples in Table 1 demonstrate the versatility of the procedure: aliphatic and aromatic aldehydes, primary and secondary amides, and urea all gave equally high yields. Most yields of **6** are significantly higher than those obtained by the comparable preparations in either AcOH or a normal Dean-Stark apparatus with benzene or toluene, e. g. 97% for **6a** and 80% for **6j** vs. 24%[6] and 48%,[4] respectively. The reactions in performance fluids are faster than those carried out in benzene or toluene with a normal Dean-Stark trap as demonstrated by the uncatalyzed reactions of 2-pyrrolidinone with benzotriazole and aldehydes. This is probably attributable to the higher concentration i.e. in performance fluid, the reaction proceeds as in the absence of solvent.

TABLE 3. ^{1}H NMR Spectral Data of Compounds **5** and **6** [(ppm), J(Hz)]

Cmpd	Benzotriazole					NCH_2Bt			
	H4	H5	H6	H7	NH	or NCHBt	R	R^1	R^2
5a[a,b]	8.52 (d, 7.5)	8.07[c]	7.75 (t, 7.5)	8.02[c]	6.24(d, 8.1, 1H)	6.60-6.80 (m, 1H)		7.27-7.5 (m, 9H)	
5b[b,d]	8.02 (d, 7.4)	7.40 (t, 8.1)	7.37-7.4[c]	7.69 (d, 7.4)	4.70, 4.93 (d, 10.1, 1H)	5.90-6.02 (m, 1H)	0.78 (d, 7.3, 3H) 1.23 (d, 7.3, 3H)	4.71 (s, 1H)	2.16 (s, 3H), 6.6 (d, 8.1, 2H), 6.9 (d, 8.1, 2H)
6a	8.43 (d, 8.1)	8.01 (t, 8.1)	8.05 (t, 8.1)	8.14 (d, 8.1)	10.5 (d, 8.5, 1H)	8.00[c] (d, 8.5, 1H)	8.33 (d, 8.5, 2H) 7.75 (d, 8.5, 2H)	–	7.43-7.53 (m, 5H)
6b	8.03 (d, 7.5)	7.34 (t, 7.5)	7.48 (t, 7.5)	7.96 (d, 8.3)	8.39 (t, 6.7)	6.31 (d, 6.7, 2H)	–	8.39 (t, 6.7, 1H)	2.34 (s, 3H), 7.18 (d, 8.3, 2H), 7.83 (d, 8.3, 2H) 6.8-6.0 (m, 2H)
6c	8.02 (d, 7.4)	7.38 (t, 8.1)	7.47 (t, 7.7)	7.95 (d, 8.6)	7.77 (t, 6.4)	6.03 (d, 6.4, 2H)	–	–	6.8-6.9 (m, 2H)
6d	8.10 (d, 7.2)	7.39[c]	7.46[c]	7.55 (d, 8.4)	–	8.08[c] (s, 1H)	7.18-7.21 (m, 2H), 7.36-7.47 (m, 3H)	2.01-2.08 (m, 2H), 2.40-2.60 (m, 2H), 3.44-3.49 (m, 1H), 3.66-3.72 (m, 1H)	
6e	8.06 (d, 8.4)	7.39 (t, 7.1)	7.51 (t, 7.1)	7.83 (d, 8.3)	–	6.40 (d, 11.0, 2H)	3.60-3.67 (m, 1H), 1.15 (d, 6.7, 3H), 0.86 (d, 6.7, 3H)	3.20-3.32 (m, 2H), 1.80-2.12 (m, 2H), 2.20-2.44 (m, 2H)	
6f	8.03 (d, 8.3)	7.39 (t, 7.4)	7.51 (t, 7.1)	7.96 (d, 8.3)	–	6.10 (s, 2H)	–	3.46 (t, 7.1, 2H), 2.41 (t, 7.9, 2H), 2.00 (quintet, 7.6, 2H)	
6g[b,e]	8.10 (d, 8.4)	7.48 (t, 7.1)	7.35[c]	7.67 (d, 8.3)	–	8.75 (s, 1H) 8.72 (s, 1H)	7.3-7.4 (m, 5H)	1.72-1.84 (m, 2H), 2.44-2.61 (m, 4H), 3.37-3.49 (m, 2H)	
6h	8.05 (d, 8.3)	7.50 (t, 7.0)	7.38 (t, 7.4)	7.84 (d, 8.4)	–	7.10 (d, 11.0, 1H)	3.44-3.52 (m, 1H), 0.89 (d, 6.6, 3H), 1.14 (d, 6.4, 3H)	1.53-1.78 (m, 4H), 2.32-2.58 (m, 2H), 3.14-3.32 (m, 2H)	
6i	8.06 (d, 8.3)	7.39 (t, 8.2)	7.51 (t, 7.5)	7.79 (d, 8.3)	–	6.99 (d, 11.0, 1H)	3.15-3.30 (m, 1H), 0.95 (d, 6.3, 3H), 1.13 (d, 6.8, 3H)	0.15-0.28 (m, 1H), 1.24-1.29 (m, 1H), 1.4-1.7 (m, 4H), 2.57 (dd, 6.6, 7.9, 2H), 3.46 (dd, 15.1, 9.8, 1H), 3.62 (dd, 15.2, 5.3, 1H),	
6j	8.02-8.08[c]	7.45-7.52[c]	7.45-7.52[c]	8.02-8.08[c]	–	6.39 (s, 2H)	–	3.03 (s, 3H)	7.39-7.40 (m, 5H)

a) Mixture of 1- and 2-benzotriazolyl isomers in a 1:3 ratio. b) Benzotriazole signals of 2-benzotriazolyl isomers: **5a**:7.83-7.87 (m, 2H), 7.30-7.36 (m, 2H); **5b**: 7.83-7.86 (m, 2H), 7.30-7.37 (m, 2H); **6g**: 7.89-7.92 (m, 2H), 7.29-7.24 (m, 2H). c) Overlapped signals. d) Mixture of 1- and 2-benzotriazolyl isomers in a 1:2 ratio. e) Mixture of 1- and 2-benzotriazolyl isomers in a 3:1 ratio.

Performance fluids provide a new organic reaction medium which has several advantages for the preparation of benzotriazole derivatives: i) the reactions are faster and the yields are higher

than reported in previous methods; ii) the reactions are more convenient to work up; iii) performance fluids, when used in conjunction with a reversed Dean-Stark trap, provide a new type of water-removal system; iv) performance fluids can be reused. These features presumably extend to other organic reactions in performance fluids and therefore, are of potential industrial interest.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were run on a Varian VXR300 instrument at 300 and 75 MHz, respectively, with TMS as the internal standard. Deuterochloroform was used as a solvent unless otherwise specified. Melting points were determined on a hot-stage apparatus. Elemental analyses were run on a Carlo Erba 1106 Elemental Analyzer.

General Procedure for the Preparation of Benzotriazole Derivatives (5a-b).- A mixture of benzotriazole (1.19 g, 10 mmol), aldehyde (10 mmol), amine (10 mmol) and strongly acidic cationic resin Amberlyst®15 (0.1g) was heated under reflux together with 5 mL of performance fluid (available from 3M company) in a 50 mL round bottom flask fitted with a reversed Dean-Stark device. After refluxing for the appropriate time (Table 1), water (0.2 mL) was removed from the trap. The mixture was allowed to cool and the solid was separated from the performance fluid by filtration. The product was dissolved in benzene (100 mL), the resin filtered off and the solvent removed to give the product.

General Procedure for the Preparation of Benzotriazole Derivatives (6a-j).- A mixture of benzotriazole (1.19g, 10 mmol), aldehyde (10 mmol), amide (10 mmol) and strongly acidic cationic resin Amberlyst®15 (0.1g) was heated under reflux together with 5 mL of performance fluid (available from 3M company) in a 50 mL round bottom flask fitted with a reversed Dean-Stark device (the synthesis of adducts **6b-c, f** and **j** was carried out using 1-hydroxymethyl-1*H*-benzotriazole (1.49g, 10 mmol) in place of benzotriazole and formaldehyde). After refluxing for the appropriate time (Table 1), water (0.2 mL) was removed from the trap. The mixture was allowed to cool and the solid was sepa-

TABLE 4. Elemental Analyses for the Novel Benzotriazole Derivatives **5a-b** and **6b-e, g-i.**

	Found %			Calculated %		
Cpmd	C	H	N	C	H	N
5a	71.85	5.07	23.38	71.74	5.02	23.24
5b	72.52	7.19	19.87	72.83	7.19	19.98
6b	67.71	5.31	21.14	67.65	5.30	21.04
6c	49.98	4.82	36.89	50.26	4.74	36.63
6d	69.47	5.57	19.37	69.85	5.52	19.16
6e	64.88	7.05	21.81	65.09	7.02	21.69
6g	70.46	5.90	18.50	70.57	5.92	18.29
6h	66.17	7.46	20.76	66.15	7.40	20.57
6i	66.90	7.76	19.68	67.11	7.74	19.56

rated from the performance fluid by filtration. The product was dissolved in chloroform (100 mL), the resin filtered off and the solvent removed to give the product. The adducts **6g-i** were recrystallized from hexane: EtOAc = 1:1.

Acknowledgment.- We thank Dr. Dong-Wei Zhu and Dr. George G. I. Moore for useful discussions and the 3M Company for providing us with performance fluids.

REFERENCES

1. D.-W. Zhu, *Synthesis*, 953 (**1993**).

2. A. R. Katritzky, S. Rachwal and G. J. Hitchings, *Tetrahedron*, **47**, 2683 (1991) and refs. cited therein.

3. A. R. Katritzky, S. Rachwal and B. Rachwal, *J. Chem. Soc. Perkin Trans. 1*, 799 (**1987**).

4. A. R. Katritzky, G. Yao, X. Lan and X. Zhao, *J. Org. Chem.*, **58**, 2086 (1993).

5. A. R. Katritzky, K. Yannakopoulou, P. Lue, D. Rasala and L. Urogdi, *J. Chem. Soc. Perkin Trans. 1*, 225 (**1989**).

6. A. R. Katritzky, J. Pernak, W.-Q. Fan and F. Saczewski, *J. Org. Chem.*, **56**, 4439 (1991).

7. J. H. Burckhalter, V. C. Stephens and L. A. R. Hall, *J. Am. Chem. Soc.*, **74**, 3868 (1952).

(Received March 11, 1994; in revised form September 19, 1994)