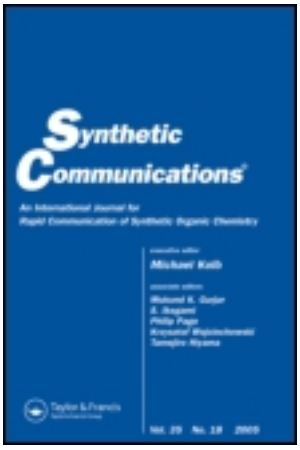


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Pentafluorophenol: A Superior Reagent for Condensations in Heterocyclic Chemistry

Vasanthakumar P. Rajappan [a] & Ramachandra S. Hosmane [a]

[a] Laboratory for Drug Design & Synthesis Department of Chemistry and Biochemistry, University of Maryland, Baltimore County 1000 Hilltop Circle, Baltimore, Maryland, 21250

Version of record first published: 02 Sep 2006.

To cite this article: Vasanthakumar P. Rajappan & Ramachandra S. Hosmane (1998): Pentafluorophenol: A Superior Reagent for Condensations in Heterocyclic Chemistry, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:4, 753-764

To link to this article: http://dx.doi.org/10.1080/00397919808005949

SYNTHETIC COMMUNICATIONS, 28(4), 753-764 (1998)

PENTAFLUOROPHENOL: A SUPERIOR REAGENT FOR CONDENSATIONS IN HETEROCYCLIC CHEMISTRY

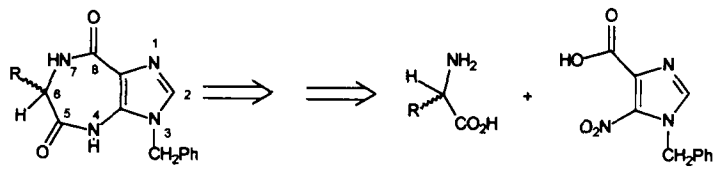
Vasanthakumar P. Rajappan and Ramachandra S. Hosmane*

Laboratory for Drug Design & Synthesis
Department of Chemistry and Biochemistry
University of Maryland, Baltimore County
1000 Hilltop Circle, Baltimore, Maryland 21250

ABSTRACT: The use of pentafluorophenol as a superior reagent for heterocyclic condensations, where other traditional condensing agents such as DCC and CDI failed, has been demonstrated.

As part of our broad research program aimed at synthesis and biological investigations of various 5,7-fused heterocycles as ring-expanded analogues of purines,[1] it became necessary to synthesize compounds of general structure **1** containing a variety of substitutions at position 6. A plausible synthetic strategy for **1** involved condensation of 1-benzyl-4-carboxy-5-nitroimidazole (**3**) with appropriately 2-substituted amino acids (**2**), followed by reduction of the nitro group and ring-closure. The most common reagents employed for such condensations in heterocyclic chemistry include

* The author to whom the correspondence should be addressed



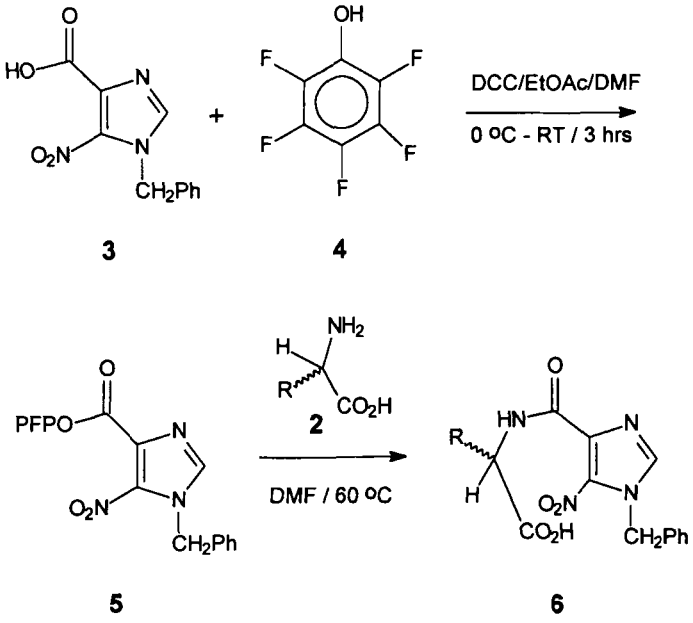
1 2 3

1,3-dicyclohexylcarbodiimide (DCC), 1,1'-carbonyldiimidazole (CDI), and a host of isosters and analogues of DCC and CDI, *e.g.* 1,1'-thiocarbonyldiimidazole (TCDI) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (EDCI). However, all our efforts to condense **2** with **3** using either DCC or CDI under a variety of experimental conditions, including the near reflux temperature of DMF, only resulted in the recovery of starting materials. The reason for failure is believed to be the zwitterionic nature of the amino acids (**2**), whose amine groups lack adequate nucleophilicity to attack the intermediate aminoimidate or imidazolyl ester. This is further corroborated by the fact that we have earlier been successful in employing both DCC and CDI in similar conditions, but using amino acid esters.[2] Using acids instead of esters has many advantages in that a wide variety of amino acids are commercially available, and that the free acids provide means for further synthetic manipulations including condensations with the desired alcohols, carboxylic acids or phenols to form reactive esters or anhydrides which would facilitate subsequent ring-closure reactions.

The use of pentafluorophenol as a condensing agent, although well-documented in peptide chemistry,[3] is seemingly rare in heterocyclic

chemistry. Because of the fact that pentafluorophenol is an excellent leaving group, our initial apprehension was the possible instability of the pentafluorophenyl anhydride derived from **3** under ambient conditions, but this turned out to be false when the reaction of **3** with pentafluorophenol (**4**), mediated by DCC, gave **5** as a stable solid in nearly quantitative yield (**Scheme 1**). Compound **5** was reacted with a variety of natural and

Scheme 1



3 **4** **5** **6**

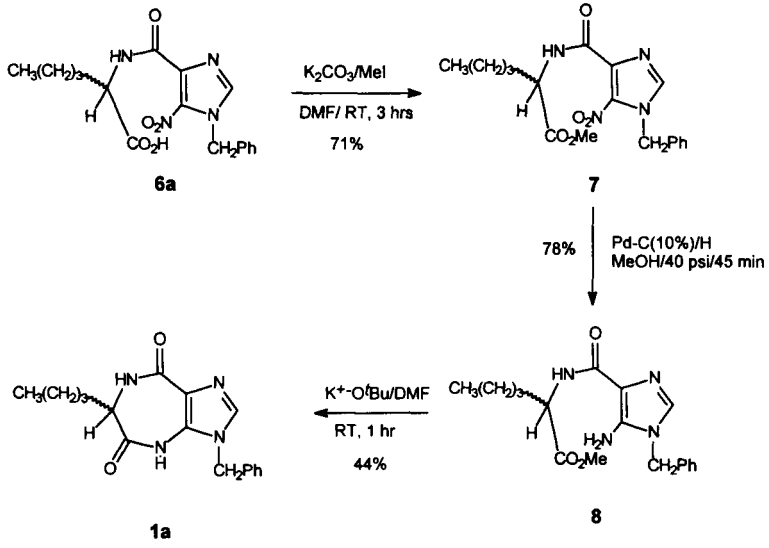
a; R = -$(CH_2)_3CH_3$
b; R = -$(CH_2)_5CH_3$
c; R = -CH_2-CH_2-$CONH_2$
d; R = -$(CH_2)_4NH$-C(O)-OCH_2Ph
e; R = -CH_2-CH_2-SCH_3

unnatural amino acids, including DL-norleucine (**2a**, R = $(CH_2)_3CH_3$), DL-2-aminocaprylic acid (**2b**, R = $(CH_2)_5CH_3$), DL-glutamine (**2c**, R = $(CH_2)_2CONH_2$), L-lysine-(ε)NH-CBz (**2d**, R = $(CH_2)_4NH$-CBz), and L-methionine (**2e**, R = $(CH_2)_2SCH_3$) to obtain the corresponding amides **6a-6e**. The reaction procedure, product isolation, as well as purification were simple, easy and convenient. A typical reaction procedure involved heating the reaction mixture in dimethylformamide at 60 °C for 3-4 hours, cooling, filtering off the slight excess of the amino acid employed, evaporation of the solvent, followed by trituration of the residue with diethyl ether. The latter process removes the highly ether-soluble pentafluorophenol formed during the reaction, yielding practically pure **6** in excellent to quantitative yields. The products were characterized by spectroscopic and microanalytical analyses.

In order to test the feasibility of using **6** to synthesize the target compound **1** for fulfillment of our main objective, compound **6a** was subjected to sequential reactions (**Scheme 2**), including esterification with methyl iodide, in the presence of potassium carbonate, to produce **7**, reduction by catalytic hydrogenation with palladium/charcoal to produce **8**, and ring-closure with potassium *t*-butoxide, to afford **1a** as a colorless solid.

In conclusion, pentafluorophenol is an excellent condensing agent which can be effectively and conveniently employed in heterocyclic

Scheme 2



condensations, especially those involving zwitterionic amino acids or related species with compromised nucleophilic character.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a General Electric QE-300 (300 MHz) instrument. The spectral data are reported in the following format: chemical shift (all relative to Me_4Si as an internal reference standard unless otherwise indicated), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplet, q = quartet, m = multiplet, and b = broad), integration, coupling constants, exchangeability after D_2O addition, and assignment of resonances. Element Microanalyses were performed by

Atlantic Microlab, Inc., Norcross, Georgia. Ultraviolet spectra were recorded on a Gilford response UV/VIS spectrophotometer. The mass spectra were recorded at the Mass Spectral Facility, Department of Biochemistry, Michigan State University. Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} (0.2 mm thickness) plates. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Anhydrous THF was freshly distilled from sodium. Anhydrous DMF and ether were purchased from Aldrich Chemical Co.

Pentafluorophenyl 1-Benzyl-5-nitroimidazole-4-carboxylate (5). To a stirred ice cooled solution of **3**[2a] (600 mg, 2.4 mmol) and pentafluorophenol (442 mg, 2.4 mmol) in a mixture of ethyl acetate (10 mL) and DMF (6 mL), 1,3-dicyclohexylcarbodiimide (495 mg, 2.4 mmol) was added with stirring and stirring was continued for 3 hours at 0 °C and 1 hour at room temperature. Dicyclohexylurea was filtered off and the solvent was evaporated in vacuo. The residue was triturated with *n*-hexane and the off-white solid separated was filtered to get 950 mg (95%) of **5**, mp. 115-117 °C; ^{1}H NMR (DMSO-d_6) δ 8.2 (s, 1H, CH), 7.3 (m, 5H, Ar-H), 5.2 (s, 2H, CH); ^{13}C NMR (DMSO-d_6) δ 140.77, 134.90, 129.11, 128, 127.56, 127.34, 50.90, 50.43; MS (FAB) *m/z* 225 (MH^+).

Anal. Calcd. for $C_{17}H_8N_3O_4F_5$: C, 49.41; H, 1.95; N, 10.17. Found: C, 49.90; H, 2.20; N, 10.25.

DL-[*N*-(1-Benzyl-5-nitroimidazolyl-4-carbonyl)]norleucine (6a). Compound **5** (413 mg, 1 mmol) and DL-norleucine (147 mg, 1.1 mmol) were taken in 5 mL of dry DMF in a flame-dried 25 mL R.B. flask, fitted with a condenser, and kept under nitrogen. The mixture was stirred at 60 °C for 3-4 hours. The reaction mixture was allowed to cool to room temperature and filtered to remove any unreacted amino acid. The solvent was rotary evaporated to get a gummy residue which upon trituration with ether afforded a light yellow powder, yield 300 mg (83%), mp 203 °C; ^{1}H NMR (DMSO-d_6) δ 8.72 (d, J = 7.8 Hz, 1H, NH, ex./w D_2O), 8.27 (s, 1H, CH), 7.37-7.10 (m, 5H, Ar-H), 5.51 (s, 2H, NCH_2), 4.53 (dt, 1H, CH), 1.68 (m, 2H, CH_2), 1.29 (m, 4H, 2xCH_2), 0.84 (t, 3H, CH_3).

Anal. Calcd. for $C_{17}H_{20}N_4O_5$: C, 56.66; H, 5.59; N, 15.55. Found: C, 56.61; H, 5.56; N,15.51.

DL-2-[*N*-(1-Benzyl-5-nitroimidazolyl-4-carbonyl)amino]caprylic Acid (6b). Compound **5** (413 mg, 1mmol) and DL-2-Aminocaprylic acid (174 mg, 1.1 mmol) were reacted using the procedure given above for **6a** to obtain 310 mg (79.9 %) of **6b** as a light yellow powder, mp 138-139 °C; ^{1}H NMR (DMSO-d_6) δ 12.72 (br, s, COOH, ex./w D_2O), 8.72 (d, J = 8.1 Hz, 1H, NH, slow ex./w D_2O), 8.27 (s, 1H, CH), 7.3 (m, 5H, Ar-H), 5.54 (s, 2H, NCH_2), 4.3 (dt, 1H, CH), 1.7 (m, 2H, CH_2), 1.2 (m, 8H, 4xCH_2), 0.8 (t, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 172.94, 160.6, 140.2, 135.51, 128.99-126.99, 51.70, 50.17, 30.98, 28.11, 25.05, 21.88, 13.81.

Anal. Calcd. for $C_{19}H_{24}N_4O_5$: C, 58.75; H, 6.23; N, 14.42. Found: C, 58.75; H, 6.25; N,14.34.

DL-[*N*(α)-(1-Benzyl-5-nitroimidazolyl-4-carbonyl)]glutamine (6c). Compound **5** (413 mg, 1mmol) and DL-Glutamine (146 mg, 1 mmol) were condensed using the procedure given above for **6a** to obtain 282 mg (75 %) of **6c** as a light brown powder, mp 186-188 °C; ^{1}H NMR (DMSO-d_6) δ 12.75 (br s, COOH, ex./w D_2O), 8.8 (d, J = 7.5 Hz, 1H, NH, slow ex./w D_2O), 8.28 (s, 1H, CH), 7.48-7.27 (m, 5H, Ar-H), 5.53 (s, 2H, NCH_2), 4.3 (dt, 1H, CH), 2.12 (t, 2H, CH_2), 1.96(m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 173.34, 172.63, 160.48, 139.92, 135.45, 128.73-126.99, 51.71, 50.16, 31.16, 26.71.

Anal. Calcd. for $C_{16}H_{17}N_5O_6$: C, 51.20; H, 4.57; N, 18.66. Found: C, 51.27; H, 4.63; N,18.75.

DL-[*N*(α)-(1-Benzyl-5-nitroimidazolyl-4-carbonyl)]-[*N*(ε)-(benzyloxycarbonyl)]lysine (6d). Compound **5** (413 mg, 1mmol) and L-lysine-NH(ε)CBz (308 mg, 1.1 mmol) were condensed using the procedure described above for **6a** to obtain 421 mg (82.5 %) of **6d** as a yellowish brown foam, mp 60-62 °C; ^{1}H NMR (DMSO-d_6) δ 8.64 (d, J = 7.8 Hz, 1H, NH, ex./w D_2O), 8.26 (s, 1H, CH), 7.45-7.26 (m, 10H, Ar-H), 5.53 (s, 2H, NCH_2), 4.98(s, 2H, OCH_2), 4.33(m, 1H, CH), 2.95 (m, 2H, CH_2), 1.71(m, 6H, 3xCH_2); ^{13}C NMR (DMSO-d_6) δ 172.94, 160.54, 156.01, 140.77, 139.35, 137.23, 135.48, 128.72, 126.57, 65.05, 51.80, 50.18, 30.67, 28.92, 22.51.

Anal. Calcd. for $C_{25}H_{27}N_5O_7$•0.5 H_2O: C, 57.85; H, 5.39; N, 13.49. Found: C, 57.72; H, 5.64; N, 12.91.

DL-[*N*-(1-Benzyl-5-nitroimidazolyl-4-carbonyl)]methionine (6e). Compound **5** (413 mg, 1mmol) and DL-Methionine (149.21 mg, 1 mmol)

were condensed using the procedure described above for **6a** to obtain 298 mg (78.4 %) of **6e** as a light yellow powder, mp 158-160 °C; ^{1}H NMR (DMSO-d_6) δ 8.81 (d, J = 8.1Hz, 1H, NH, ex./w D_2O), 8.28 (s, 1H, CH), 7.36-7.18 (m, 5H, Ar-H), 5.54 (s, 2H, NCH_2), 4.51-4.46 (dt, 1H, CH), 2.5 (t, 2H, CH_2), 2.02(m, 5H, CH_2 & CH_3); ^{13}C NMR (DMSO-d_6) δ 172.71, 160.79, 140.28, 137.20, 135.60, 128.80-127.06, 51.03, 50.26, 30.74, 29.57, 14.51.

Anal. Calcd. for $C_{16}H_{18}N_4O_5$: C, 50.79; H, 4.79; N, 14.81; S, 8.47. Found: C, 50.80; H, 4.85; N, 14.72; S, 8.39.

Methyl 2-[*N*-(1-Benzyl-5-nitroimidazolyl-4-carbonyl)amino]hexanoate (7). To a solution of **6a** (388 mg, 1 mmol) dissolved in 4 mL of DMF, was added potassium carbonate (181mg, 1.5mmol) and methyl iodide (162 µL, 2.60 mmol). After 3 hours, water (25 mL) was added, and the reaction mixture was extracted with $CHCl_3$ (3 x 15 mL). The $CHCl_3$ extract was dried ($MgSO_4$) and filtered. The filtrate was rotary evaporated to obtain a gummy residue. Ice was added to the residue to obtain a white solid which was filtered and dried under vacuum to get 285 mg (71%) of crude **7**. It was recrystallized from 2-propanol/water, mp 95 °C; ^{1}H NMR (DMSO-d_6) δ 8.8 (d, J = 7.8 Hz, 1H, NH, ex./w D_2O), 8.28 (s, 1H, CH), 7.37-7.20 (m, 5H, ArH), 5.54 (s, 2H, NCH_2), 4.42 (q, J = 5.4 & 8.4 Hz, 1H, CH), 3.64 (s, 3H, OCH_3), 1.69 (m, 2H, CH_2), 1.28 (m, 4H, 2xCH_2), 0.84 (t, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{22}N_4O_5$: C, 57.75; H, 5.92; N, 14.96. Found: C, 57.77; H, 5.98; N, 14.85.

Methyl2-[*N*-(5-Amino-1-benzylimidazolyl-4-carbonyl)amino]hexa-

noate (8). Compound **7** (200 mg, 1.87 mmol) was dissolved in 50 mL of methanol, and Pd-C(10%) (75 mg) was added to this solution. The mixture was hydrogenated at 40 psi in a Parr hydrogenator for 45 minutes. The reaction mixture was filtered through a pad of Celite™ and the filtrate was rotary evaporated to get 148 mg (78%) of **8** as a gummy residue which under vacuum solidified to give a foam. The amino compound was used as such for the subsequent ring-closure reaction after drying over P_2O_5, mp 72 °C; ^{1}H NMR (DMSO-d_6) δ 7.48-7.27 (m, 7H, NH, CH, ArH), 5.76 (s, 2H, NH_2, ex.*/w* D_2O), 5.25 (s, 2H, NCH_2), 4.34 (q, 1H, CH), 1.68 (m, 2H, CH_2), 1.25 (m, 4H, 2xCH_2), 0.84 (t, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{24}N_4O_3$: C, 62.71; H, 6.97; N, 16.26. Found: C, 62.69; H, 7.02; N, 16.33.

1-Benzyl-6-butyl-5,6,7,8-tetrahydro-4*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (1a). Compound **8** (100 mg, 0.26 mmol) was dissolved in 5 mL of dry DMF in a flame-dried flask kept under nitrogen atmosphere. To this solution was added 0.4 mL of a 1*M* solution of potassium *tert*-butoxide in THF. The solution turned deep red. It was allowed to stir at room temperature for 3 hours. The reaction progress was monitored by tlc (4:1 $CHCl_3$-MeOH), which showed a slower moving spot than the starting material. The solvent was rotary evaporated and the residue was loaded on a flash silica gel column. The product was eluted using a mixture of $CHCl_3$-MeOH (12:1). Evaporation of the solvent, followed by trituration with diethyl ether afforded 40 mg (44%) of pure **1a**, mp 301 °C; ^{1}H

NMR(DMSO-d_6) δ 9.91 (br, s, 1H, NH, ex./w D_2O), 7.71 (d, J = 5.1 Hz, 1H, NH, ex./w D_2O), 7.67 (s, 1H, CH), 7.30-7.13 (m, 5H, ArH), 5.24 (s, 2H, NCH_2), 3.60 (m, 1H, CH), 1.65 (m, 2H, CH_2), 1.25 (m, 4H, $2xCH_2$), 0.81 (t, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{24}N_4O_3$: C, 65.37; H, 6.45; N, 17.94. Found: C, 65.47; H, 6.48; N, 18.03.

ACKNOWLEDGMENTS

This research was supported by grants (#RO1 GM49249 and #RO1 CA 71079) from the National Institutes of Health. The Michigan State University Mass Spectrometry Facility was supported in part from a grant (# P41RR00480-0053) from the National Institutes of Health.

REFERENCES

1. (a) Bhan, A. and Hosmane, R. S. *Syn. Commun.* **1995**, *25*, 2723; (b) Bhan, A. and Hosmane, R.S. *Tetrahedron Lett.* **1994**, *35*, 6831; (c) Wang, L., Bhan, A., Hosmane, R.S. and Guiles, R.D. *Nucleosides & Nucleotides* **1994**, *13*, 2307.

2. (a) Bhan, A. and Hosmane, R.S., *J. Heterocycl. Chem.* **1993** , *30*, 1453; (b) Bhan, A. and Hosmane, R.S., *Nucleosides & Nucleotides* **1992**, *11*, 1175; (c) Hosmane, R. S., Bhan, A., Hulce, M., Zhang, H. M. and Hosmane, N. S. *Nucleosides & Nucleotides* **1991**, *10*, 819; (d) Hosmane, R.S., Bhan, A., Karpel, R.L., Siriwardane, U., Zhang, H.

and Hosmane, N.S., *J. Org. Chem.* **1990**, *55*, 5882;

3. Kizafaludi, L., Roberts, J.E., Johnson, R.H., Mayers, G.L. and Kovacs, J. *J. Org. Chem.* **1970**,*35*, 3563.

(Received in the USA 13 August 1997)