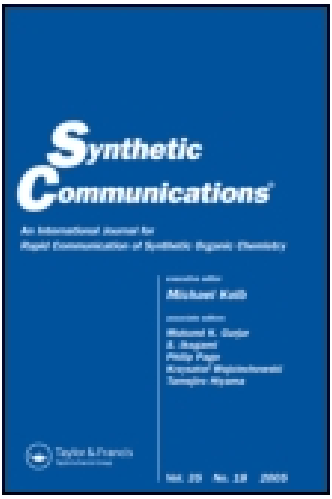

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 09 Nov 2006.

To cite this article: Chaitanya G. Dave & Vaishali A. Parikh (2001) HETEROCYCLIZATION USING PHASE TRANSFER CATALYSIS: A SIMPLE AND CONVENIENT SYNTHESIS OF 2-AMINO-1-ARYL-5-OXO-4,5-DIHYDRO-1H-PYRROLE-3-CARBONITRILES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:9, 1301-1306, DOI: 10.1081/SCC-100104038

To link to this article: http://dx.doi.org/10.1081/SCC-100104038

SYNTHETIC COMMUNICATIONS, 31(9), 1301–1306 (2001)

HETEROCYCLIZATION USING PHASE TRANSFER CATALYSIS: A SIMPLE AND CONVENIENT SYNTHESIS OF 2-AMINO-1-ARYL-5-OXO-4,5-DIHYDRO-1H-PYRROLE-3-CARBONITRILES

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ABSTRACT

A simple and convenient synthesis of 2-amino-1-aryl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitriles has been studied with and without phase transfer conditions. The best results were obtained using 18-crown-6 under solid-liquid phase transfer conditions in acetonitrile.

o-Aminonitriles are important building blocks for the construction of a variety of fused heterocycles.[1] Schafer and Gewald[2] have reported the synthesis of 2-amino-1-aryl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitriles in varying yields of 33–75%. Phase transfer catalysis (PTC) has many advantages over conventional homogeneous methodologies.[3–5] The use of PTC in the reactions involving heterocyclic compounds are extremely

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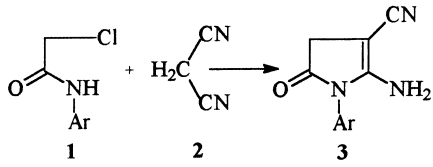
diverse,[6–8] heterocyclizations under PT conditions have a great scope[9] as little attention is attributed to such reactions.

In continuation of our interest in the use of PTC in heterocycles,[10] we report a simple and cleaner method for the synthesis of 2-amino-1-aryl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitriles via heterocyclization under solid-liquid PT conditions with good yields. A comparison with phase transfer catalysts such as tetrabutylammonium bromide (TBAB), tetrabutylammonium hydrogen sulfate ($TBHSO_4$), triethylbenzylammonium chloride (TEBA) under liquid-liquid PTC, and 18-crown-6 using solid-liquid PTC and without phase transfer catalyst has been undertaken.

The reactions between *N*-aryl-2-chloroacetamids (**1**) and malononitrile (**2**) where carried out without PTC and with PTC at room temperature under liquid-liquid and solid-liquid phase transfer conditions to get 2-amino-1-aryl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitriles. (**3**). The reactions employing quaternary ammonium salts (TBAB, $TBHSO_4$, TEBA) as catalysts were performed in methylene chloride, whereas acetonitrile was used as a solvent for 18-crown-6. TBAB and TEBA are not the catalyst of choice for this particular heterocyclization, whereas the use of $TBHSO_4$ in equimolar ratio with the reactants yielded compounds **3** in 50–63% yields.[11,12] The best results were obtained for **3** with 68–83% yields when the reactions were performed in acetonitrile using 18-crown-6 as catalyst and powdered KOH as a base at room temperature.[13] In the conventional method,[2] when a mixture of *N*-aryl-2-chloroacetamides (**1**), malononitrile (**2**), and potassium carbonate was refluxed in ethanol, the target 2-amino-1-aryl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitriles[3] were not obtained generally in good yields. Further, this conventional method is not as clean as PTC methodology, which is evident from the melting point range reported (Tab. 1).



1 **2** **3**

Looking to the mechanistic aspect of this process, the initial *C*-alkylation of active methylene group of malononitrile (**2**) should have taken place with **1**, followed by the heterocyclization step, which is supposed to proceed via an intramolecular nucleophilic addition of -NH-Ar onto the nitrile group to give an imine that could yield an enamine and also aromatic system for the formation of o-aminonitrile system. A comparison of the results obtained without and with PT catalysis using $TBHSO_4$ and 18-crown-6 has been depicted in Table 1.

Table 1. Preparation of 2-Amino-1-aryl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitriles 3

Entry	Ar	Without PTC[a]		With PTC				M.p.°C Observed (reported)[a]
				$TBHSO_4$[b]		18-Crown-6[c]		
		Yield (%)	Time (min)	Yield (%)	Time (h)	Yield (%)	Time (min)	
3a	C_6H_5	75	30	60	3.0	75	40	218–220 (215–220)
3b	4-$CH_3C_6H_4$	33	30	55	3.0	75	40	258–260 (230–240)
3c	4-$OCH_3C_6H_4$	43	30	53	2.5	78	30	204–206 (203–208)
3d	4-ClC_6H_4	45	30	56	3.0	72	40	210–212 (220–226)
3e	4-BrC_6H_4	45	30	58	3.0	70	40	221–223 —
3f	4-FC_6H_4	43	30	52	3.0	70	30	230–232 —
3g	4-IC_6H_4	40	30	50	3.5	68	40	215–217 —
3h	3-Cl-4-FC_6H_3	50	30	63	2.5	83	30	225–227 —

All the compounds gave satisfactory elemental analysis (within ±0.4%). [a]ref. 2; [b]Solvent: CH_2Cl_2; [c]Solvent: CH_3CN.

In conclusion, we have described a simple and convenient synthesis of 2-amino-1-aryl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitriles, which are important building blocks for the construction of various fused heterocycles. A comparison of conventional method, liquid-liquid PTC, and solid-liquid PTC suggests that the solid-liquid PT conditions using 18-crown-6 is the method of choice with better yields.

EXPERIMENTAL

Synthesis of 2-Amino-1-aryl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitriles (3)

Typical Procedure 1 (Liquid-Liquid PT Condition)

To the stirred mixture of dichloromethane (15 mL), KOH solution (5 mL, 50% w/v), and $TBHSO_4$ (3.39 g, 0.01 mol) was added malononitrile (**2**, 0.792 g, 0.01 mol) at room temperature. To this was added *N*-aryl-2-chloroacetamides[14] (**1**, 0.01 mol) portionwise. The reaction mixture was stirred further at room temperature for 2.5–3.5 h (TLC). The organic phase was separated, washed with water, acetic acid (10% v/v), and again with water. The solvent was distilled under reduced pressure and cooled to 5°–10°C, the solid thus obtained was filtered and crystallized from a mixture of acetonitrile and ethanol (6:4).

Typical Procedure 2 (Solid-Liquid PT Condition)

To the stirred mixture of acetonitrile (15 mL), KOH (0.700 g, 0.012 mol), and 18-crown-6 (0.120 g, 10 mol%) was added malononitrile (0.330 g, 0.005 mol) and stirred for 10 m. To this was added *N*-aryl-2-chloroacetamides[14] (**1**, 0.005 mol) portionwise. The reaction mixture was further stirred at room temperature for 30–40 min (TLC). The solvent was distilled under reduced pressure and the reaction mixture was poured onto crushed ice (20 g), neutralized with acetic acid (50% v/v) and kept at room temperature for 3 h. The products thus obtained were crystallized from the mixture of acetonitrile and alcohol (6:4). The selected spectroscopic data of compounds **3** are given.

2-amino-5-oxo-1-(4-methylphenyl)-4,5-dihydro-1H-pyrrole-3-carbonitrile (3b)

M.p. 258°–260°C (lit.[2] 230°–240°C); IR (KBr) cm^{-1}: 3428 and 3298 (NH_2), 2210 (CN), 1714 (C = O); ^1H NMR (300 MHz, $CDCl_3$+$DMSOd_6$) δ:

2.31 (s, 3H, CH_3), 3.25 (s, 2H, CH_2), 6.72 (s, 2H, NH_2), 7.10–7.74 (m, 4H, Ar-H).

2-amino-5-oxo-1-(4-bromophenyl)-4,5-dihydro-1H-pyrrole-3-carbonitrile (3e)

M.p. 221°–223°C; IR (KBr) cm^{-1}: 3431 and 3277 (NH_2), 2207 (CN), 1720 (C = O); ^1H NMR (300 MHz, $CDCl_3$+$DMSOd_6$) δ: 3.35(s, 2H, CH_2), 6.37 (s, 2H, NH_2), 7.16–7.75 (m, 4H, Ar-H).

2-amino-5-oxo-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrrole-3-carbonitrile (3f)

M.p. 230°–232°C; IR (KBr) cm^{-1}: 3378 and 3268 (NH_2), 2200 (CN), 1713 (C = O); ^1H NMR (300 MHz, $CDCl_3$+$DMSOd_6$) δ: 3.36 (s, 2H, CH_2), 6.26 (s, 2H, NH_2), 7.12–7.71 (m, 4H, Ar-H). MS (70 eV) *m/z* (%): 277 (79.9, M^+), 249 (22.1), 197 (38.4), 170 (100), 278 (49.9, M+1).

2-amio-5-oxo-1-(4-iodophenyl)-4,5-dihydro-1H-pyrrole-3-carbonitrile (3g)

M.p. 215°–217°C; IR (KBr) cm^{-1}: 3380 and 3298 (NH_2), 2205(CN), 1715(C = 0); ^1H NMR (300 MHz, $CDCl_3$+ $DMSOd_6$) δ : 3.32 (s, 2H, CH_2), 6.28 (s, 2H, CH_2), 7.13–7.72 (m, 4H, Ar-H).

2-amino-5-oxo-1-(3-chloro-4-fluorophenyl)-4,5-dihydro-1H-pyrrole-3-carbonitrile (3h)

Mp. 225–27°C I(KBr)cm: 3410 and 3332(NH_2), 2211 (CN), 1720 (C = O); ^1H NMR (300 MHz, $CDCl_3$+$DMSOd_6$) δ: 3.34 (s, 2H, CH_2), 6.60 (s, 2H, NH_2), 7.20–7.42 (m, 3H, Ar-H).

ACKNOWLEDGMENTS

We thank RSIC, Chandigadh, India, for ^1H NMR and mass spectra and Dishman Pharmaceuticals and Chemicals, Ahmedabad, India, for the gift of Phase Transfer Catalysts.

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Received in the UK May 30, 2000