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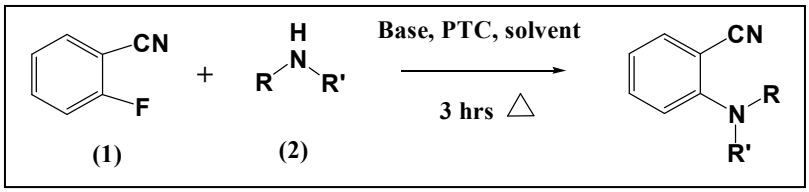

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ARTICLE TYPE

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N-arylation of amines with fluorobenzonitriles in aqueous medium is described. A mixture of N,N diisopropylethyl amine and Na_2CO3 (1:1) is found to achieve maximum conversion by refluxing 3 hours in water. The product can be easily isolated by solvent extraction.

N-arylation of amines is an important C-N bond forming process in pharmaceutical research.[1] Usually these compounds are synthesized *via* aromatic nucleophilic substitution reaction (S_NAr) of amines[2] with aryl halides or *via* transition metal mediated cross-coupling reaction.[3] Transition metal catalyzed N-arylation has some drawbacks in industrial applications as the metal catalysts are expensive, oxygen sensitive, and toxic. Hence metal catalyst free S_NAr should be reactions of choice. But electron rich aromatic compounds are generally unreactive toward nucleophilic substitution. Hence electron poor aryl electrophiles with one or more strong electron withdrawing groups have been substrates of choice.[4a-f] Fluorobenzonitriles are widely used substrates for S_NAr, but reported methods have several draw backs including low yield, use of high boiling organic solvents and reaction at elevated temperature.[4g-i] In our recent attempts to develop new green protocols[5] and to improve arylation of amines[6], we used mixed organic and inorganic bases for S_NAr reaction. Herein we describe a simple, high yielding, metal catalyst free N-arylation reaction in water in which fluorine is replaced from fluorobenzonitriles by using mixed organic and inorganic bases in presence of a phase transfer catalyst (PTC).

During the course of our ongoing research activity on bioactive compounds, we were exploring suitable protocols to synthesize 2,4-diaminoquinazolines. Quinazolines and quinazolones are bioactive molecules also part of various natural products and drugs.[7] Among the quinazolines, 2,4-diaminoquinazolines are very important pharmacophore present in many marketed drugs such as prazosin,[8a] methotrexate,[8b] trimetrexate,[8c] and piritrexim.[8d] They have shown significant biological activities such as anticancer,[9a] SMN2 promoter,[9b] dihydrofolate reductase (DHFR) inhibitor,[9c] kinase inhibitor and opioid receptor like-1 (ORL1) antagonists.[9d]

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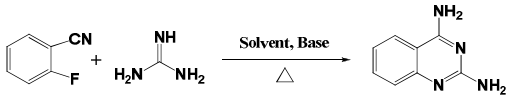
Traditionally, 2,4-diaminoquinazolines are synthesized by reacting 2-fluorobenzonitrile with guanidine carbonate at elevated temperature *via* aromatic S_NAr reaction.[10] Alternatively, they can also be synthesized by Cu-catalyzed Ullmann type N-arylation of 2-bromobenzonitrile with guanidine.[11]

Table 1. Varying reaction conditions for quinazoline synthesis[a]



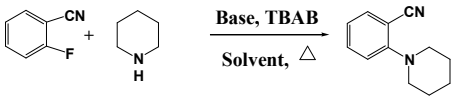
React[n] code	Inorganic base (mol %)	Organic base (mol %)	Temp (^{0}C)	Time (hrs)	Yield[b].
a	0		140	8	37
b	Na_2CO_3(100)		140	8	72
c	Na_2CO_3(100)		60	8	0
d	K_2CO_3(100)		140	8	25
e	$NaHCO_3$(100)		140	8	55
f		DBU (100)	60	8	0
g		DBU (100)	100	8	0
h		DBU (100)	140	8	31
i		DBN (100)	140	8	22
j		TEA (100)	125	8	0
k		DIPEA (100)	125	8	63
l	Na_2CO_3(100)		125	8	10
m	Na_2CO_3(90)	DIPEA (10)	125	3	45
n	Na_2CO_3(70)	DIPEA (30)	125	3	48
o	Na_2CO_3(50)	DIPEA (50)	125	3	79
p	Na_2CO_3(30)	DIPEA (70)	125	3	63
q	Na_2CO_3(10)	DIPEA (90)	125	3	55
r[c]	Na_2CO_3(50)	DIPEA (50)	100	8	0

[a] Reaction conditions: 2-fluorobenzonitrile (1mmol), guanidine carbonate (1mmol), base (2equiv; organic/inorganic), DMA (3mL), reaction time 3h. DMA: N,N-dimethylacetamide, DIPEA: Diisopropylethylamine, DBU: 1, 8-diazabicyclo [5.4.0] undec-8-ene, DBN:1,5-diazabicyclo[4.3.0]non-5-ene, TEA: triethylamine.
[b] Isolated yield.
[c] Reaction medium: Water

The reaction was optimized using 2-fluorobenzonitrile as substrate and guanidine carbonate as nucleophile. The first reaction was carried out with reference to a reported method in

N,N dimethylacetamide (DMA) at reflux condition with moderate yield[12] (Table 1, entry a,). With the introduction of a base, the yield of the reaction improved significantly (entry b). However this reaction was not feasible at lower temperature (entry c). Several inorganic and organic bases were tried at elevated temperature from which Na_2CO_3 and diisopropylethylamine (DIPEA) were found to give good yield. Reaction in presence of DIPEA was carried out at 125^0C. The yield was found slightly less than the same reaction carried out in presence of Na_2CO_3 (entry l). Then we thought to use a mixture of Na_2CO_3 and DIPEA in order to see the effect on yield (entry m to q). A very significant improvement in yield was observed when both the bases were used in 1:1 mole ratio (entry o). With this encouraging result, we tried to explore the greener aspect of this reaction by replacing DMA with water. To our disappointment the reaction didn't proceed even at reflux condition (entry r). The reason may be attributed to the very high water solubility of guanidine carbonate and poor water solubility of 2-fluorobenzonitrile. This solubility difference may keep these two reactants in immiscible phases due to which the reaction didn't occur at all even in presence of tetrabutylammoniumbromide (TBAB), a phase transfer catalyst (PTC)

Table 2. Varying reaction conditions for S_NAr reaction[a]

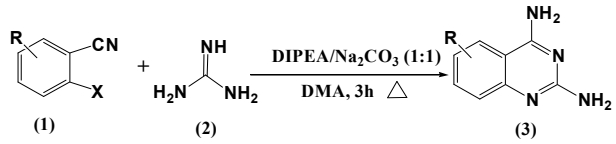


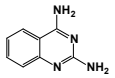
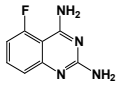
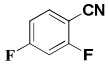
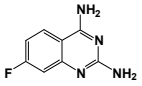
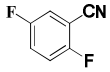
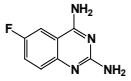
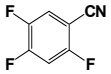
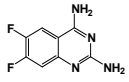
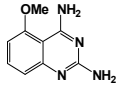
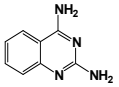
Entry	Solvent	Temp (^{0}C)	Organic base	Inorganic base	TBAB (mol%)	Yield[%][b]
a	Water	100	DIPEA	Na_2CO_3	0	40
b	DMA	100	DIPEA	Na_2CO_3	0	88
c	Water	100	DIPEA	Na_2CO_3	5	66
d	Water	100	DIPEA	Na_2CO_3	10	83
e	DMA	140		Cs_2CO_3	0	61
f	DMA	100		Cs_2CO_3	0	35
g	Water	100	DIPEA		10	40
h	Water	100		Na_2CO_3	10	30
i	Water	30	DIPEA	Na_2CO_3	10	0
j	Water	100	DBU	Na_2CO_3	10	65
k	Water	100	DBN	Na_2CO_3	10	58
l	Water	100	TEA	Na_2CO_3	10	71

[a] Reaction conditions: 2-fluorobenzonitrile (1mmol), piperidine (1mmol), base (2equiv; organic/inorganic 1:1), solvent (3mL), reaction time 3h. DMA: N,N-dimethylacetamide, DIPEA: Diisopropylethylamine, DBU: 1, 8-diazabicyclo [5.4.0] undec-8-ene, DBN:1,5-diazabicyclo[4.3.0]non-5-ene, TEA: Triethylamine TBAB: Tetrabutylammoniumbromide.
[b] Isolated yield.

To check the feasibility of above protocol for S_NAr, a batch reaction was carried out in water using 2-fluorobenzonitrile as substrate and piperidine as nucleophile in place of guanidine carbonate. Around 40% yield was observed (Table 2, entry a). When the same reaction was carried out in DMA at 100^0C surprisingly 88% yield was recorded (entry b). Choices of solvent and base are crucial for catalyst free S_NAr reactions. Both the reactants are insoluble in water while both Na_2CO_3 and DIPEA are highly water soluble. Probably they are not available in the reaction due to phase separation. All the reactants and bases are soluble in DMA which is leading for a very good conversion. With the introduction of TBAB, a significant improvement in yield was observed in water (entry c and d). Couple of reactions were carried out with reference to a reported method in DMA by using Cs_2CO_3 as base.[2a] Moderate yield of product was observed (entry e). As the reaction was carried out in a conventional laboratory assembled reactor, some part of piperidine (bp 106^0C) might have been lost to give moderate yield (entry e). At lower temperature the yield was found even lower (entry f). Most interestingly yield was reduced, when the reaction was carried out in absence of either inorganic (entry g) or organic base (entry h). This indicated that both organic and inorganic bases are required whether the reaction was carried out either in DMA or in water. No conversion was observed when the reaction was carried out at room temperature (entry i). Organic bases like DBU, DBN, and TEA also showed promising yields (entries j and k) but DIPEA gave maximum yield among them.

Table 3. Synthesis of 2,4-diaminoquinazolines [a]



Entry	ArX (1)	Product (3)	Yield[b]
a			79
b			88
c			52
d			48
e			25
f			44
g			19

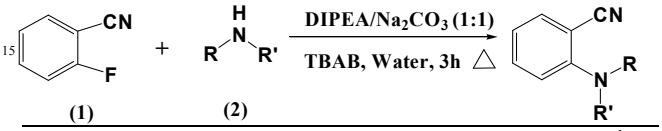
[a] Protocol 1: 2-fluorobenzonitrile (1mmol), guanidine carbonate (1mmol), base (2equiv; DIPEA/Na_2CO_3 1:1), solvent DMA (3mL), reaction time 3h at 125^0C.[15] DMA: N,N-dimethylacetamide, DIPEA: Diisopropylethylamine.
[b] Isolated Yield.

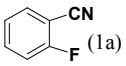
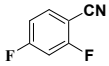
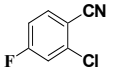
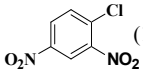
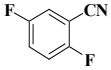
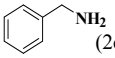
From these optimization experiments we have standardized two protocols for the synthesis of 2,4-diaminoquinazolines (protocol 1, table 3) and derivatization of fluorobenzonitriles (protocol 2, table 4). The latter one can be carried out in both DMA and

water. To study the general applicability of the present developed methods, the standardized reaction conditions were attempted with different halobenzonitriles with various amines and are presented in Table 3 and 4 respectively. As shown in the table 3, the desired 2,4-diaminoquinazolines were obtained in good to excellent yields (entries a–e). The protocol is not found effective for 2-chlorobenzonitrile (entry g).

Protocol 2 was carried out in water to check the feasibility of the green aspect. Various substrates including fluorobenzonitriles, dinitrochlorobenzene. Excellent yields were recorded in all cases (Table 4, entries a-e). Incase of fluoroquinazolines no conversion was obaserved.

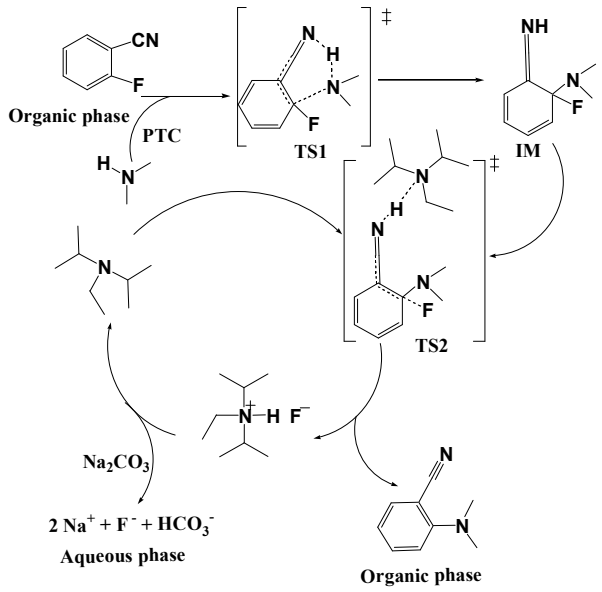
Table 4. Arylation of amines with fluorobenzonitriles[a]



Entry	ArX (1)	Amine (2)	Time	Yield[b]
a	 (1a)	 (2a)	3	83
b	 (1b)	(2a)	3	87
c	 (1c)	(2a)	3	82
d	 (1d)	(2a)	3	76
e	 (1e)	(2a)	3	81
f	 (1f)	(2a)	3	79
g	 (1g)	(2a)	8	75
h	(1a)	 (2b)	3	85
i	(1b)	 (2c)	5	79
j	(1b)	 (2d)	3	72

[a] Protocol 2: 2-fluorobenzonitrile (1mmol), piperidine (1mmol), base (2equiv; DIPEA/Na_2CO_3 1:1), water (3mL), TBAB 10 mol%, reaction time 3h at reflux.[16]
[b] Isolated Yield.

Excellent yield for 2,4-dinitrochlorobenzene was also observed (entry f). 2,5-diflurobenzonitrile (entry g) showed good conversion only after extended reaction time. This shows presence of electron withdrawing groups at 2 and 4 position are beneficial where as at 5 position it is not beneficial for product yield. This indicates that the reaction mechanism is following S_NAr pathway. Other nitrogen containing nucleophiles also witnessed good yield with this protocol (entries h to j). The products were isolated by simple solvent extraction with ethylacetate and purified by flash chromatography.



Scheme 1

The most important finding of this study is the effect of the mixture of organic and inorganic bases on yield. A plausible mechanism is attempted in scheme 1 on the basis of experimental observations, semiempirical calculations and literature report.[13]

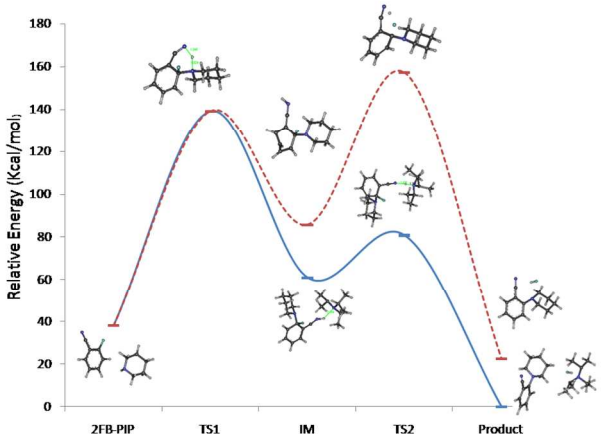


Figure 1. Relative energy of starting material, transition states and intermediates with respect to products in presence (solid line) and absence (dotted line) of DIPEA.

2-fluorobenzonitrile and piperidine react with each other to form a transition state (TS1) in the organic phase. TBAB helps the transport of amine (piperidine) as well as DIPEA from aqueous

phase to organic phase and thus plays a significant role to enhance the rate of reaction. TS1 converts to an intermediate (IM) after migration of hydrogen from amine to nitrile group. At the same time the organic base DIPEA forms a strong hydrogen bonding with the intermediate and forms another transition state (TS2). The energy of transition state in presence and absence of DIPEA was calculated by semiempirical method AM1 (Figure 1).[14] Transition state 2 (TS2) and IM are stabilized by DIPEA. The difference in transition state energy of TS2 clearly indicates the involvement of DIPEA for facilitation of the reaction. This was also reflected in the % yield of product (Table 2, entry d and entry h). As fluorine is a better leaving group in S_NAr reaction, it leaves the ring with pair of electron. Simultaneously base abstracts the hydrogen and a pair of electron is available to satisfy aromaticity. The product remains in the organic phase and the fluoride anion is sequestered out from the organic phase to aqueous phase by the cation of DIPEA. The organic base was regenerated in aqueous phase by the inorganic base Na_2CO_3 and again comes to organic phase. Thus the mixture of organic and inorganic bases enhances the yield through above mechanism.

From this study we may conclude that a mixed organic and inorganic base system is useful to achieve better yield in N-arylation of amine through S_NAr mechanism. The reaction may be carried out in aqueous medium. The inorganic base will remain in the aqueous phase to regenerate the organic base due to which the yield will increase.

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We thank Director, DRDE, Gwalior for his keen interest and encouragement.

Notes and references

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14. Spectral data and AM1 calculation availabe in supporting information.
15. **General procedure for protocol 1: Synthesis of 2,4-diaminoquinazoline:** In a round bottom flask add 3 ml N,N-dimethylacetamide (DMA), 0.001 mole of 2-fluorobenzonitrile, 0.001 mole of guanidine carbonate, 0.001 mole of N,N-diisopropylethylamine (DIPEA) and 0.001 mole of Na_2CO_3. Reaction was carried out at 125^0C in an oil bath. After 3 hours, reaction was stopped by cooling the reaction mixture. The product was precipitated out by adding 1 ml dicloromethane followed by excess hexane on an ice bath. Precipitates were separated, washed with 3 ml water and recrystalized from methanol to achive the pure product.
16. **General procedure for protocol 2: Synthesis of 2-piperidinylbenzonitrile:** In a round bottom flask add 3 ml water, 0.001 mole of 2-fluorobenzonitrile, 0.001 mole of piperidine, 0.001 mole of N,N-diisopropylethylamine (DIPEA), 0.0001 mol of ter-butylammoniumbromide (TBAB) and 0.001 mole of Na_2CO_3. Reaction was carried out at reflux for 3 hours. Then reaction mixture was cooled and extracted with ethyl acetate. The productes were purified by flash chromatography on silica by using hexane-ethylacetate mobile phase.