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A new application of diphenylphosphorylazide (DPPA) reagent: convenient transformations of quinolin-4-one, pyridin-4-one and quinazolin-4-one derivatives into the 4-azido and 4-amino counterparts ☆

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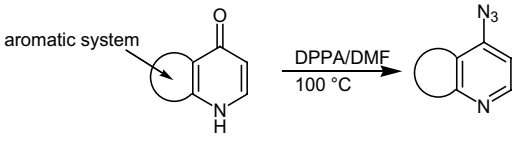
Abstract—Herein, we describe a transformation of the oxo-function of a series of quinolin/pyridin/quinazolin-4-ones into 4-azido and thence into 4-amino derivatives in moderate yields by a very short and convenient new procedure using DPPA (diphenylphosphoryl azide) as reagent. A mechanism for this interesting new application of DPPA is suggested based on the identification of some of the intermediates.

Heterocyclic aromatic aza-compounds, especially pyridine, quinoline and quinazoline derivatives, are widely used in organic synthesis and chemical technology. One of the best methods for synthesizing their amino derivatives starts from the corresponding oxy-counterparts and involves a two step process:[1,2] the oxo derivative is first transformed into a leaving group such as tosyl oxy or halogen followed by reaction with an azide anion. Catalytic reduction of the azido-derivatives obtained, results in the desired amines in good yield.[1,2] In our continuing efforts to introduce exhaustive substitution into constrained heterocyclic scaffolds, we have focused on the introduction of amino groups into quinolin-4-ones, pyridin-4-ones and quinazolin-4-ones.

DPPA has been developed and extensively used to transform acids into acyl azide intermediates, which undergo Curtius rearrangement under appropriate conditions.[3,4] It has been also applied as a peptide coupling reagent[5] and for transformation of alcohols into amines.[6] Nevertheless, to our knowledge, its reactivity towards heterocyclic oxo aromatics, that can be in equilibrium with their phenol tautomers, has not been investigated. We have reacted a variety of quinolin/pyridin/- and quinazolin-4-ones with DPPA in DMF at 100 °C for 24 h and obtained, in one-pot, the corresponding azido-derivatives in moderate yields (see Scheme 1 and Table 1).

The moderate yields can be explained firstly, as a result of steric hindrance at position 4 caused by substitution at position 3 and secondly, in terms of the low stability of aromatic azides, which undergo slow degradation especially at high temperature. The lowest yield was observed for the reaction of 2,3-diphenylquinolin-4-one (Table 1, entry 5, 22%). The reactions were followed by HPLC–MS



Scheme 1.

Keywords: DPPA; Azide; Quinolin-4-one; Pyridin-4-one; Quinazolin-4-ol.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.04.032

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0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
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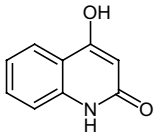
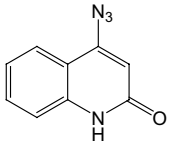
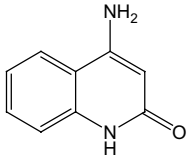
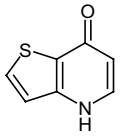
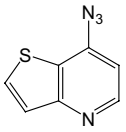
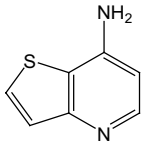
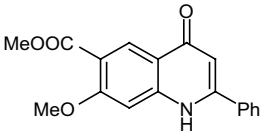
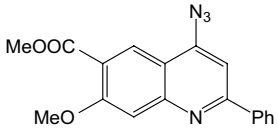
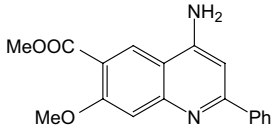
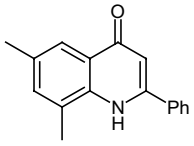
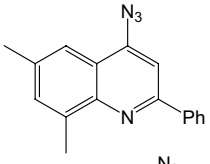
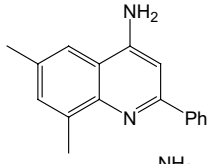
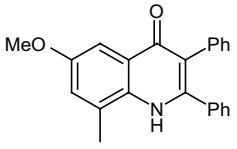
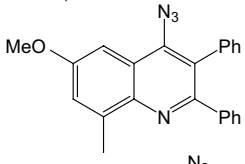
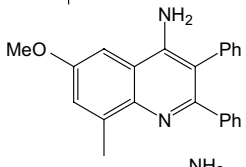
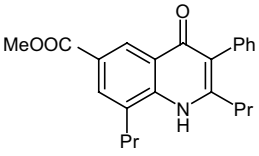
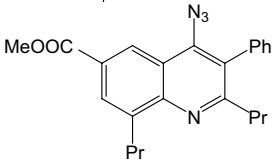
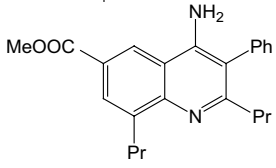
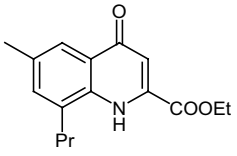
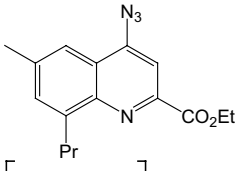
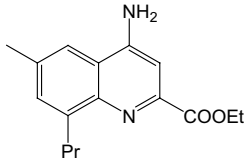
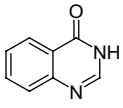
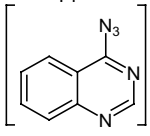
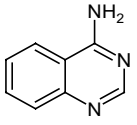
Table 1. Azides and amines synthesized using DPPA as reagent

Precursor	#	Azide	Yield (%)	#	Amine	Yield (%)
	**1**		61	**9**		84
	**2**		55	**10**		88
	**3**		64	**11**		84
	**4**		74	**12**		98
	**5**		22	**13**		97
	**6**		48	**14**		97
	**7**		45	**15**		83
	**8**		—	**16**		63 (overall yield)

analysis, which allowed the clear identification of a phosphoric ester intermediate formed from the DPPA and the oxo function in the early part of the reactions (entries 1, 3–7).[6] We suggest that this intermediate is further attacked by the azide anion to generate azido derivatives, with elimination of phosphate, mediated by a sp^3 intermediate in an addition–elimination pathway. Continuing the reactions beyond 24 h brought about an accelerated degradation of the azide products with a concomitant decrease in yields. When the reaction was performed on 2,4-dioxo derivatives (Table 1, entry 1) the azide was obtained regioselectively leaving the 2-oxo group intact. The nonreactivity of the 2-oxo position was confirmed when we tried to perform the reaction on quinolin/pyridin-2-ones without success (data not shown). 4*H*-Thieno[3,2-*b*]pyridin-7-one (Table 1, entry 2) reacted readily with DPPA to give the corresponding azide derivative. Interestingly, 4-aminoquinazoline **16** can be obtained in one-pot and in good yield (63% overall yield) without isolation of the azide intermediate **8**. Thus, amines can be directly obtained in higher yields without isolation of the intermediate azides. All the azides were transformed into amines using regular catalytic hydrogenation conditions, in high yields (Table 1, entries 9–16).

In conclusion, we have demonstrated a new application of DPPA for the transformation of various pyridin-4-ones, quinazolin-4-ones and quinolin-4-ones into their corresponding azides and thence into amines.

Extension of this approach to other oxy heterocycles is currently being investigated.

1. Experimental

1.1. Synthesis of azides 1–8

1 mmol of the 4-oxo precursor and 1.1 mmol of DPPA were dissolved in 5 mL DMF, 1.3 mmol of triethylamine was added and the mixture was heated to 100 °C with stirring under argon for 24 h. After cooling, the DMF was evaporated under vacuum and the resulting crude oil was purified by HPLC except for azide **8**, which was directly reduced without isolation. (One typical example is given, for physical data of other products see Supplementary information.)

1.2. Synthesis of amines 9–16

Azide **1**–**7** or crude **8** (0.5 mmol) was dissolved in 10 mL methanol under argon, the solution was degassed twice in vacuo and 30 mg of Pd/C was added. Reduction was carried out under hydrogen for 24 h. The Pd/C was removed by passage through Celite and the methanol evaporated in vacuo. (One typical example is given, for physical data of other products see Supplementary information.)

1.3. 4-Azido-6,8-dimethyl-2-phenyl-quinoline 4

The product was purified by preparative HPLC (RP-18). Elution started with petroleum ether and ended with petroleum ether/ethyl acetate (70:30 v/v) and used a linear gradient at a flow rate of 100 mL/min (cycle time 25 min). Analytical HPLC (t_R): 9.84 min; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 2.47 (s, 3H); 2.75 (s, 3H); 7.48–7.59 (m, 4H Ph and 7-H); 7.65 (s, 1H, 5-H); 7.94 (s, 1H, 3-H); 8.32–8.35 (m, 2H Ph). ^{13}C NMR (600 MHz, $CDCl_3$, δ ppm), 155 (2-*C*); 142 (9-*C*); 141 (1′-*C*); 138 (4-*C*); 137–137 (6-C, 8-C); 132 (7-*C*); 130 (4′-*C*); 129 (1′-*C*); 127 (2′-*C*); 117 (5-*C*); 106 (3-*C*); 22 (Me); 18 (Me). MS (electron spray, m/z): 275 $[MH]^+$.

1.4. 4-Amino-6,8-dimethyl-2-phenyl-quinoline (12)

The product was isolated without special purification. Analytical HPLC (t_R): 6.17 min; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 2.42 (s, 3H); 2.67 (s, 3H); 6.63 (s, 2H, NH_2); 7.10 (s, 1H, 3-*H*); 7.34 (s, 1H, 5-H); 7.41–7.50 (m, 4H of Ph); 7.77 (s, 1H, 7-*H*); 8.09–8.11 (m, 2H of Ph). ^{13}C NMR (600 MHz, $CDCl_3$ δ ppm), 155 (2-*C*); 146 (9-*C*); 152 (1′-*C*); 140 (4-*C*); 134–137 (6-*C*, 8-*C*); 132 (7-*C*); 129 (4′-*C*); 126 (1′-*C*); 119 (2′-*C*); 117 (5-*C*); 98 (3-*C*); 22 (Me); 18 (Me). MS (m/z): 249 $[MH^+]$. HRMS (electron spray) calcd for $C_{17}H_{16}N_2$: 248.131301 and found: 248.131349.

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