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Efficient Synthesis of *N*-Arylpiperazinones via a Selective Intramolecular Mitsunobu Cyclodehydration

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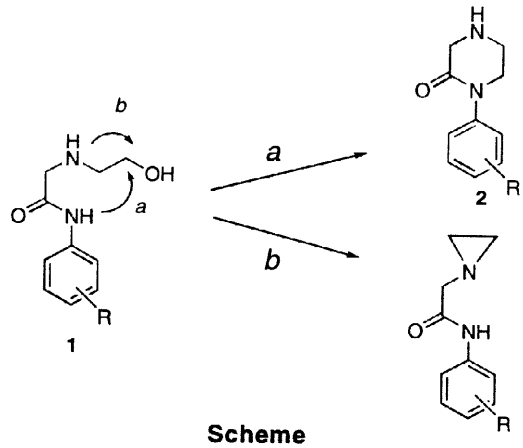
Abstract: A practical two pot synthesis of *N*-arylpiperazinones from the corresponding aniline is described. The key transformation is a selective intramolecular Mitsunobu cyclodehydration of an amidoalcohol intermediate. A series of *N*-arylpiperazinones were prepared in yields up to 89%.

Interest in the piperazinone ring system has centered on its utility as a conformationally-constrained peptidomimetic in biologically-active molecules.[1] Additionally, *N*-aryl-piperazinones are often precursors for the synthesis of medicinally important *N*-arylpiperazines via amide reduction.[2] Recent syntheses of piperazinones include the cyclization of *N*-(aminoethyl)glycinate derivatives,[1a,c,3] the condensation of *N*-(chloroethyl)glycinate with amines[4] and the condensation of monoprotected ethylenediamines with α-haloacetic acid derivatives.[1b,2a,c] Access to the glycinate and ethylenediamine precursors requires additional steps, detracting from the simplicity of these routes.[5]

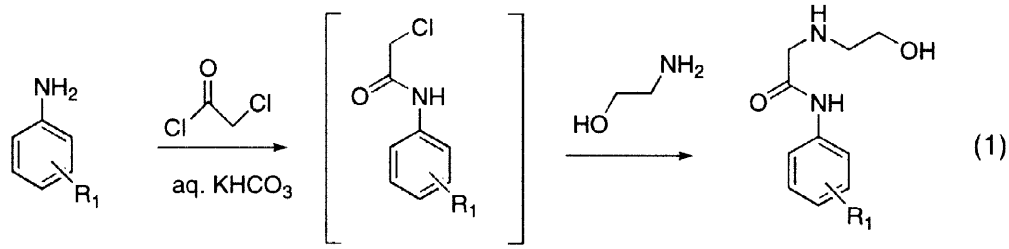
While use of the Mitsunobu reaction[6] for the synthesis of lactams from β-hydroxyamides is known,[7] those previously performed in the presence of an α-amino group have utilized protecting groups to prevent competing aziridine formation.[8] The Mitsunobu cyclodehydration of amino-hydroxyamides such as **1** can conceivably proceed via nucleophilic attack upon the oxyphosphonium intermediate either by the amido nitrogen to provide piperazinone **2** (path *a*, **Scheme**) or by the amine to give the aziridine (path *b*). However, we speculated that the increased acidity of the amido nitrogen relative to the amine may favor piperazinone formation. Herein, we describe the facile synthesis of *N*-arylpiperazinones from the corresponding anilines employing a selective Mitsunobu cyclodehydration *without the use of protecting groups at the N-4 position.*



Scheme

PII: S0040-4039(98)01670-0

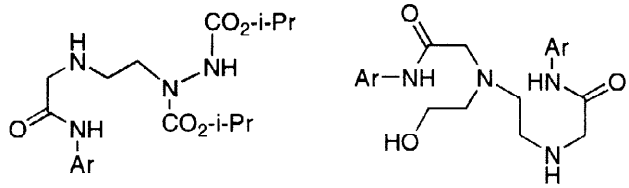
Amidoalcohol precursors **1** were prepared via acylation of the aniline precursor with chloroacetyl chloride in isopropyl acetate (IpAc) under Schotten-Baumann conditions to afford the chloroacetamide intermediates **3** (eq 1). Amination was accomplished by removing the aqueous layer followed by the addition of 4 equiv ethanolamine to the crude reaction mixture and warming to 60 °C for 1-3 h to provide **1**.[9]



(1)

The Mitsunobu dehydration of the amidoalcohols was studied with a series of phosphines and azodicarboxylate derivatives by forming the complex *in situ* in the presence of the amidoalcohol. Generally, the azodicarboxylate (diisopropyl (DIAD), di-*tert*-butyl (DBAD) or dipyrrolidinyl (DPAD)) was added to a mixture of the trialkylphosphine and **1** at 0 °C.[10] The reactions were complete within 1 h upon subsequent warming to 25 °C. The piperazinones were cleanly isolated as the HCl salts upon addition of 1 equiv ethanolic HCl to the reaction mixture. Tributylphosphine afforded the cleanest reactions, while both THF and ethyl acetate were found to be suitable solvents for the transformation. While higher yields of **1** were frequently obtained with the more hindered azodicarboxylates, DIAD was the preferred reagent due to its lower cost, bulk availability and ease of handling.

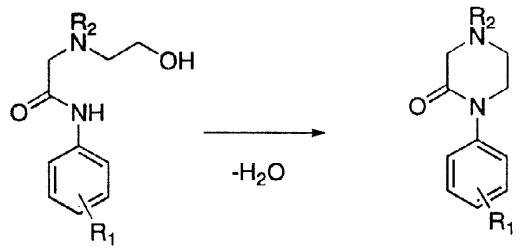
Two reaction by-products were identified; the alkylated hydrazide **4** and ethylenediamine derivative **5**, the result of an *intermolecular* dehydration. The formation of **4** appears to be minimized by the use of the bulkier azodicarboxylates, thus accounting for the improved yields with these reagents.[11]



4 **5**

The scope of this cyclodehydration methodology was expanded to a series of amidoalcohols derived from ethanolamine and 2-(methylamino)ethanol that were prepared from readily available aniline derivatives. The results are compiled in the **Table** and show the reaction to proceed under a range of substitution patterns on the aniline ring.

Table. Synthesis of N-Arylpiperazinones (**2**) via Mitsunobu Cyclodehydration[a]



1 **2**

Substrate	Ar Substitution (R_1)	R_2	% Yield of **2**
1a	4-Cl	H	72 [b,f]
1b	3-Cl	H	87 [b,e]
1c	2-Cl	H	83 [c,f]
1d	3-OCF_3	H	76 [b,f]
1e	H	H	83 [d,e]
1f	H	Me	89 [d,e]
1g	3-OMe	H	84 [d,e]
1h	3-Br	H	88 [b,f]
1i	4-OMe	H	82 [d,e]
1j	3-Cl, 4-Me	H	74 [b,e]
1k	3-NO_2	H	81 [b,e]

[a]All reactions performed in EtOAc (0.4-0.5 M) at 0-5 °C using 1.3 eq Bu_3P and the indicated azodicarboxylate. Unless otherwise noted, the Mitsunobu complex for all reactions was formed *in situ*. [b]di-t-butylazodicarboxylate. [c]preformed Mitsunobu complex with DIAD. [d]1,1'-(azocarbonyl)dipiperidine. [e]assay yield. [f]isolated yield.

In conclusion, an efficient synthesis of *N*-arylpiperazinones utilizing a selective Mitsunobu cyclodehydration has been developed. Isolation was effected as the piperazinone•HCl salts in good to excellent yields.

Synthesis of 1-(3-Bromophenyl)piperazinone HCl (1h): Amidoalcohol **2h**[12] (5.0 g) was combined with EtOAc (32 ml) and tributylphosphine (6.4 ml) in a nitrogen-purged vessel at 2 °C. Di-t-butylazodicarboxamide (5.9 g dissolved in 20 ml EtOAc) was added dropwise over 20 min. The reaction mixture was aged at 5 °C for 15 min and then warmed to 40 °C. Ethanolic HCl (5.0 ml; 4.2N solution) was added dropwise over 1 h. The

resulting slurry was cooled to 5 °C over 1 h and aged for 1 h. The product was isolated by filtration and washed with chilled EtOAc (2 x 10 ml). Drying *in vacuo* at 40 °C for 18 h provided **1h** (4.6 g; 88% yield) as colorless solid; ^{13}C NMR(75 MHz; DMSO-d_6): δ_C 162.1, 142.8, 131.0, 129.9, 128.9, 125.0, 121.2, 46.1, 44.9, 39.8.

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References and Notes

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9. Isolated yields of **1a-k** generally ranged from 54-94% and are unoptimized.

10. In one example (entry **1c**), it was advantageous to pre-form the Mitsunobu complex at 0 °C (15 min age) and then add it to a slurry of the amidoalcohol in EtOAc.

11. We have been unable thus far to observe or isolate any aziridine intermediates in the cyclodehydration step.

12. Synthesis of amidoalcohol (**1h**): 3-bromoaniline (35.0 g) was combined with IpAc (210 ml) and 20% aq potassium bicarbonate (173 g). The biphasic mixture was cooled to 5 °C and treated with chloroacetyl chloride (19.5 ml) dropwise over 30 min. The reaction mixture was warmed to 25 °C and the aqueous layer removed. The organic layer was combined with ethanolamine (43 ml), heated to 60 °C and aged for 2 hr. Water (60 ml) and IpAc (25 ml) were added to the reaction mixture. The solution was reheated to 60 °C and the aqueous layer removed. The organic layer was cooled to 0 °C over 1 h and aged for 1 h. The solids were collected and washed with chilled IpAc (3 x 30 ml). The product was dried in vacuo at 40 °C to a constant weight to provide 36.2 g of **1h** (66%); ^{13}C NMR (75 MHz; DMSO-d_6): δ_C 170.9, 140.2, 130.6, 125.8, 121.5, 121.38, 117.9, 60.3, 52.7, 51.5.