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One pot conversion of azido arenes to *N*-arylacetamides and *N*-arylformamides: synthesis of 1,4-benzodiazepine-2,5-diones and fused [2,1-*b*]quinazolinones

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Abstract—Sodium iodide in acidic media has been employed for the synthesis of *N*-arylformamides and *N*-arylacetamides. The NaI/acetic acid reagent system has also been extended for the synthesis of 1,4-benzodiazepine-2,5-diones, pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones, and fused [2,1-*b*]quinazolinones.

1. Introduction

In recent years, azides[1] have attracted much attention not only as excellent protecting groups, but also as key intermediates for the synthesis of a large number of organic compounds such as nucleosides, carbohydrates,[2] and *N*-containing heterocycles[3] like quinolines, quinazolines, benzodiazepines, lactams, and cyclic imides. The conversion of azido arenes to *N*-acylated intermediates has been a desirable strategy in various synthetic sequences. *N*-Arylacetamides and *N*-arylformamides have been widely used as intermediates for the synthesis of biologically active compounds such as chemotherapeutic and antibacterial agents[4] and in the synthesis of isocyanides and allylated carbonyl compounds.[5] Several methods have been reported[6] for the synthesis of these compounds from the amine precursors while very few methods are available in the literature[7] for the direct conversion of azides in to *N*-acylamines. The majority of these methods have shortcomings in relation to their general applicability, selectivity, longer reaction times, and ease of handling. In view of these factors, there has been considerable demand for the development of novel and efficient methods for the preparation of these compounds.

As a part of our continuing research toward the synthesis of heterocyclic natural products, we have reported[8] various methods for azide group reduction. Recently we have also reported[9] the preparation of *N*-arylformamides from the corresponding azides employing a microwave-assisted Zn–ammonium formate system.

In continuation of these efforts, we herein report the preparation of *N*-arylformamides/*N*-arylacetamides employing NaI in the presence of formic acid and acetic acid, respectively. Additionally, we also report an azide reductive-cyclization process for the synthesis of 1,4-benzodiazepine-2,5-diones and fused [2,1-*b*]quinazolinones using NaI in acetic acid. This reagent system has been recently reported[10] for the ring opening of cyclopropanes.

2. *N*-Acylation of azides

N-Acylamines have been synthesized from azides using $RuCl_3$–thioacetic acid[11] or AlI_3–acetic anhydride.[12]

In the former case the use of thioacetic acid is often found to be inconvenient due to its noxious smell and $RuCl_3$ is very expensive. The latter reagent system

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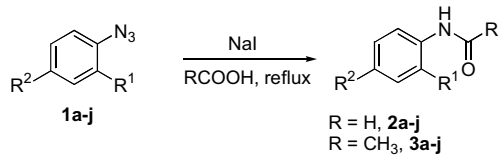


Scheme 1.

Table 1. Synthesis of *N*-arylformamides **2** and *N*-arylacetamides **3** employing NaI in formic acid and acetic acid, respectively

Product	Substrate		R	Time (h)	Yield[a,b] (%)
	R^1	R^2			
2a	H	Cl	H	3.5	90
2b	H	Br	H	5	80
2c	H	F	H	3	90
2d	H	CH_3	H	4	80
2e	H	OCH_3	H	4	85
2f	H	OH	H	3.5	80
2g	Cl	H	H	4	85
2h	CH_3	H	H	3.5	75
2i	$COCH_3$	H	H	5	74
2j	COPh	H	H	4.5	70
3a	H	Cl	CH_3	3	85
3b	H	Br	CH_3	4.5	70
3c	H	F	CH_3	3	88
3d	H	CH_3	CH_3	3.5	75
3e	H	OCH_3	CH_3	3	80
3f	H	OH	CH_3	3	70
3g	Cl	H	CH_3	4	78
3h	CH_3	H	CH_3	3.5	75
3i	$COCH_3$	H	CH_3	5	73
3j	COPh	H	CH_3	4	70

[a] Isolated yields.
[b] Compounds characterized by ^{1}H NMR, EIMS, and by comparison with authentic samples.

employs moisture sensitive AlI_3. In view of these disadvantages, we herein report the reductive acylation of azides employing NaI in acetic acid and NaI in formic acid to obtain *N*-arylacetamides and *N*-arylformamides, respectively, as shown in Scheme 1.

The azide precursors **1a**–**j** have been found to undergo acetylation/formylation under reflux for 3-4 h in 70–90% yield as shown in Table 1. Selectivity toward *N*-acylation against *O*-acylation was clearly evident as seen in the entries **2f** and **3f**. These reductive acylations could have been initiated by the in situ generation of HI, as mentioned in our previous report.[13] It is interesting to note that azides **3a**–**e** have been reduced to the corresponding amines by employing this reagent system at room temperature.

3. Synthesis of 1,4-benzodiazepinediones and fused [2,1-*b*]quinazolinones

Benzodiazepines are an important class of compounds with biological activities ranging from CNS depressant to anti-cancer,[14a] anti-HIV,[14b] and anti-Alzheimer.[14c] Another important class of compounds, fused [2,1-*b*]-quinazolinones, especially vasicinone and its analogues have also been reported to possess various pharmacological properties such as bronchodilation,[15a] antitumor,[15b] and antimycobacterial.[15c] Moreover, azido reductive-cyclization especially the aza-Wittig approach[16] has been an important strategy for the synthesis of these *N*-containing heterocycles.

As a part of our efforts for the synthesis of *N*-containing heterocycles, we have developed novel and versatile methods through the azide reductive route. In this connection we have earlier reported the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines (PBD) and fused [2,1-*b*]-quinazolinones employing TMSCl–NaI,[8a] $FeSO_4$,[8b] $FeCl_3$–*N*,*N*-dimethylhydrazine,[8c] HMDST,[8d] $FeCl_3$–NaI,[8e] HI,[13] and baker's yeast.[8f,g] Continuing our efforts in this direction, we have employed NaI/AcOH for the synthesis of 1,4-benzodiazepine-2,5-diones and fused [2,1-*b*]quinazolinone systems. Precursors *N*-(2-azidobenzoyl)-amino acid methyl esters **6**, **10**, and *N*-(2-azidobenzoyl) lactams **14** readily cyclized to the corresponding 1,4-benzodiazepinediones **7** (Table 2), **11** (Table 3), and fused [2,1-*b*]quinazolinone **15** (Table 4), respectively, as shown in Schemes 2–4. Further, the products **7b**–**i** exhibited significant optical rotations and chiral HPLC analysis of these diones indicated no notable racemization.

This method is an efficient and convenient alternative to the aza-Wittig approach employing triphenylphosphine or tributylphosphine as it does not require anhydrous conditions and further, the reagent system is inexpensive. Additionally, 1,4-benzodiazepine-2,5-diones were obtained directly unlike in the former case, which

Table 2. Synthesis of 1,4-benzodiazepine-2,5-diones **7** by employing NaI in acetic acid

Product	R	Yield[a,b] (%)	$[\alpha]_D^{26}$ (*c* 0.5, MeOH)
7a	H	81	—
7b	CH_3	75	+421
7c	$CH(CH_3)_2$	70	+92
7d	$CH_2CH(CH_3)_2$	80	+221
7e	$CH(CH_3)CH_2CH_3$	75	+60
7f	CH_2Ph	76	+175
7g	(±)Ph	78	—
7h	(+)Ph	78	+67
7i	(−)Ph	78	−66

[a] Isolated yields.
[b] Compounds characterized by ^{1}H NMR, EIMS.

Table 3. Synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones **11** employing NaI in acetic acid

Product	X	Yield[a,b] (%)
11a	H	96
11b	5-CH_3	92
11c	4-Cl	90

[a] Isolated yields.
[b] Compounds characterized by ^{1}H NMR, EIMS.

Table 4. Synthesis of fused [2,1-*b*]quinazolinones **15** employing NaI in acetic acid

Product	R^1	R^2	*n*	Yield[a,b] (%)
15a	H	H	1	95
15b	CH_3	H	1	95
15c	H	Cl	1	94
15d	H	H	2	90
15e	CH_3	H	2	88
15f	H	Cl	2	87
15g	H	H	3	90
15h	CH_3	H	3	93
15i	H	Cl	3	95

[a] Isolated yields.
[b] Compounds characterized by ^{1}H NMR, EIMS.

afforded imino-ether derivatives in 16–84 h. These were further converted to the 1,4-benzodiazepine-2,5-diones in TFA–H_2O–THF in 1:1:12.5 for 7 h at room temperature. Further it was an interesting observation that the precursor **6a**–**i** did not cyclize with methods previously reported[8] by us.

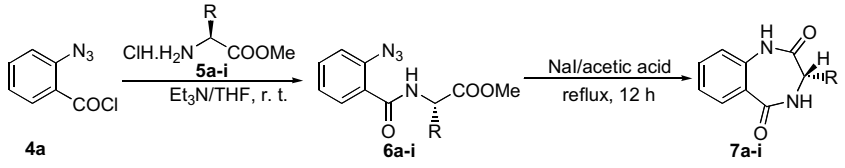
This method has also been extended for the synthesis of the pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione ring system (PBD dilactams). These molecules are known to be noncovalent interactive minor groove binders. These are also the intermediates for the synthesis of structurally modified PBD imines via oxidation of secondary amines[17a] or by reduction of *N*-protected dilactams.[17b] Further, they exhibit different types of biological properties such as antiphase activity, analgesic antagonist, anti-inflammatory, psychomotor depressant activity, and herbicidal properties.[18]

In conclusion, we have demonstrated an efficient, cost-effective, and ecofriendly protocol for the synthesis of *N*-arylacetamides and *N*-arylformamides. Further, this method has been successfully applied to the synthesis of pharmacologically important *N*-containing heterocycles namely 1,4-benzodiazepine-2,5-diones, pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones, and fused [2,1-*b*]quinazolinones.

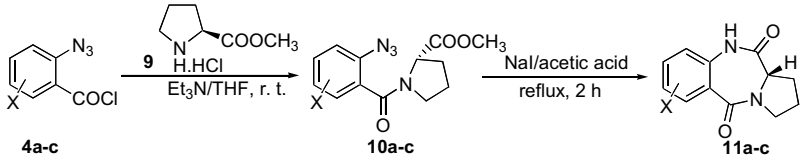
4. Typical procedure

Compound **7i**: To a solution of **6i** (1 mmol) in acetic acid (10 mL) was added sodium iodide (10 mmol). The resulting mixture was stirred at reflux for 12 h. The solvent was then removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with aq $NaHCO_3$ solution and aq $Na_2S_2O_3$ followed by brine. The ethyl acetate fraction was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue thus obtained was purified over silica gel using ethyl acetate–hexane (1:1) to afford pure **7i**. ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.00–5.10 (d, 1H, J = 6 Hz), 6.90–7.50 (m, 8H), 7.71 (d, 1H, J = 6.5 Hz), 8.95 (d, 1H, J = 7.7 Hz), 10.6 (s, 1H); EIMS *m*/*z* 252 (M^+).

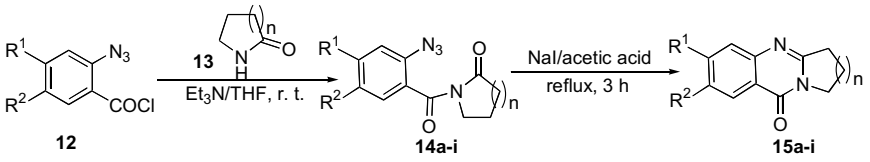
Compound **15a**: This compound was obtained following the above procedure using compound **14a** but refluxing for 3 h. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.3 (dd, 2H, J = 7.5 and 8.0 Hz), 3.2 (t, 2H, J = 8.0 Hz), 4.2 (t, 2H, J = 7.5 Hz), 7.5 (t, 1H, J = 7.4 Hz), 7.6–7.8 (m, 2H), 8.3 (d, 1H, J = 8.0 Hz); EIMS *m*/*z* 186 (M^+).



Scheme 2.



Scheme 3.



Scheme 4.

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