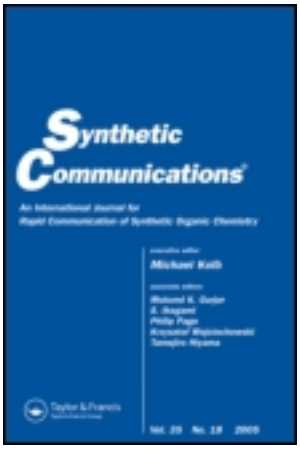

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Direct Synthesis of N-Acylalkylenediamines from Carboxylic Acids Under Mild Conditions

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Direct Synthesis of *N*-Acylalkylenediamines from Carboxylic Acids Under Mild Conditions

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ABSTRACT

Monoacylated piperazine derivatives were prepared directly from carboxylic acids and piperazine using triphenylphosphine (TPP) and *N*-bromosuccinimide (NBS) in dichloromethane. Inexpensive and readily available reagents, excellent yields, short reaction times and mild reaction conditions are important features of this method.

Key Words: Monoacylated derivatives of diamines; Triphenylphosphine; *N*-bromosuccinimide; Carboxylic acids.

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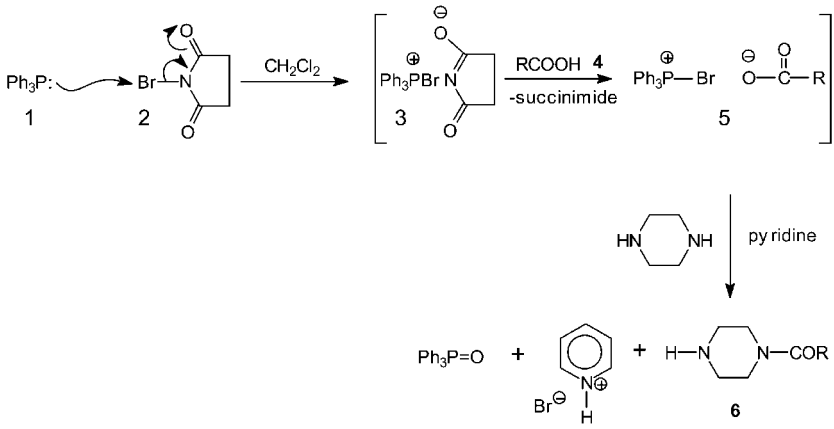
INTRODUCTION

The importance of monoacylated piperazine derivatives in materials and medicinal chemistry has developed various methods for their preparation. The method involving the conversion of esters to amides is somewhat limited because it requires either drastic conditions[1] or special reagents[2–8] that may interfere with other functional groups in the molecule. Milder catalysts such as 2-pyridone[9] and boron tribromide[10] have also been used; however, the generality of these reactions has not been examined. Another method using activated amines such as tin,[11] titanium,[12] and aluminium[13] amides has been addressed; however, no practical technique is available for the synthesis of tertiary amides. Direct monoacylation of symmetrical diamines becomes frequently problematic due to competitive bis-acylation.[14] For instance, under normal basic conditions, the bis-adduct is isolated as the major product. A possible explanation for the uncontrollable bis-acylation of the symmetrical secondary diamines under these conditions is that the monobenzoylated intermediate is more soluble in the solvent than piperazine and it reacts preferentially with the aryl carboxyl derivative to provide the observed bis-acylated product. Therefore, a number of indirect multistep processes have been developed,[15a–d] which involve protecting one of the nitrogen atoms, acylating the other and deprotecting to give the desired products. The same objective was also achieved by a rather laborious procedure involving the addition of starting materials in several batches with very cautious control of the pH value of the reaction system.[15e] The problem of bis-acylation can be somewhat circumvented using recently reported methods.[16–18] However, these methods suffer from drawbacks, such as the use of a strongly basic lithium reagent, drastic reaction conditions, long reaction times, the use of aggressive and expensive reagents, application to limited substrates, and difficulties in separation/purification of the products. Therefore, it is of interest to develop an alternative process for efficient, rapid and selective preparation of monoacylated piperazine derivatives under mild conditions.

In this communication, we report the use of triphenylphosphine (TPP) with *N*-bromosuccinimide (NBS) for the selective monoacylation of piperazine under mild reaction conditions (Sch. 1).

EXPERIMENTAL

The carboxylic acid was first activated with TPP and NBS to furnish intermediate, (**5**) which was further treated with piperazine to afford monoacylated piperazine under mild reaction conditions. This method converts carboxylic



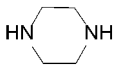
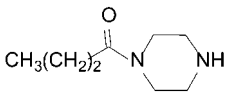
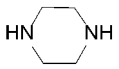
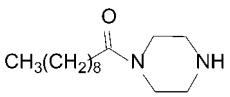
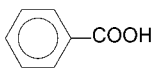
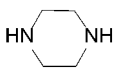
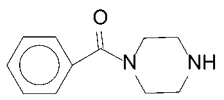
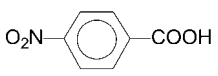
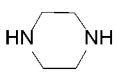
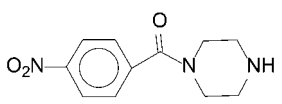
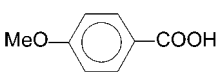
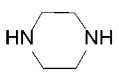
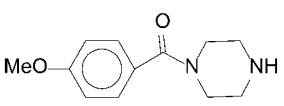
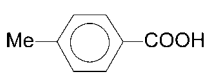
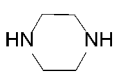
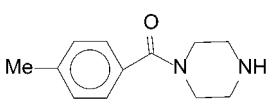
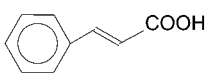
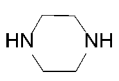
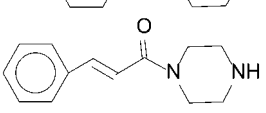
Scheme 1.

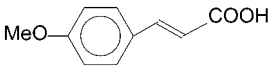
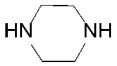
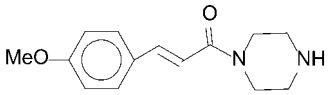
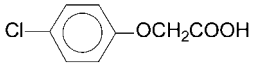
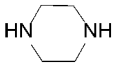
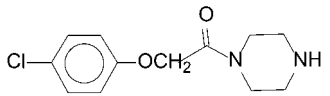
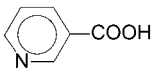
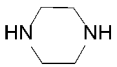
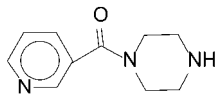
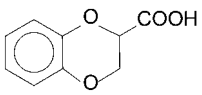
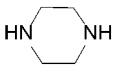
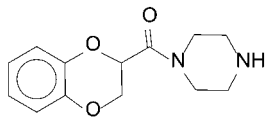
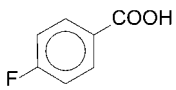
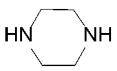
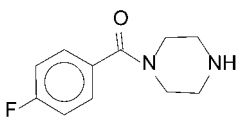
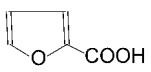
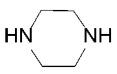
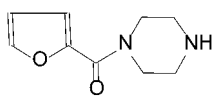
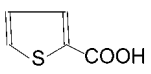
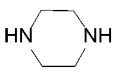
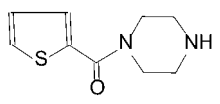
acid group into the amide moiety in a one-pot synthesis at room temperature. The desired monoacylated product, (**6**) could easily be purified by simple recrystallization or using silica gel chromatography. The byproducts such as TPP oxide and pyridinium hydrobromide were easily removed by filtration followed by aqueous work-up. The ^{1}H NMR revealed that the formation of monoacylated piperazine derivative. The methodology was found to be general, a variety of carboxylic acids, such as aliphatic, unsaturated, aromatic, and heterocyclic acids were smoothly converted into the corresponding mono-acylated piperazine derivatives. We prepared *N*-acylalkylenediamine (entry k), an useful precursor of the popular antihypertensive drug Doxazosin, in 96% yield at room temperature in 30 min. The recently reported method[1] for this compound required 3 hr and at 110°C with 61% yield. Various diamines (entries p–u) were examined for this transformation and it was found to work satisfactory. In conclusion, a convenient and straightforward protocol has been developed to convert piperazine into monosubstituted piperazine derivatives (Table 1).

Typical Procedure

A mixture of 2,3-dihydrobenzo[1,4]dioxin-carboxylic acid (180 mg, 1 mmol) and triphenylphosphine (527 mg, 2 mmol) in dichloromethane (10 mL) was cooled to 0–5°C. The NBS (410 mg, 2.5 mmol) was added and the reaction mixture was stirred for 15 min. A mixture of piperazine (86 mg, 1 mmol) and pyridine (197 mg, 2.5 mmol) was added to the above reaction mixture at room temperature and stirring was continued for 30 min. After

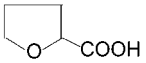
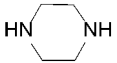
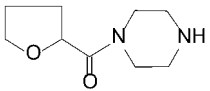
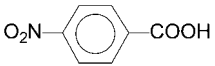
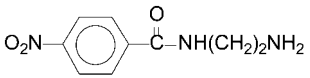
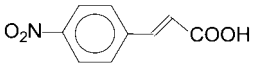
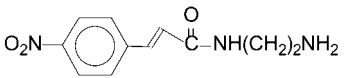
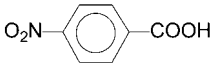
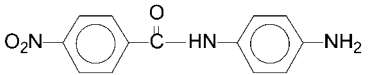
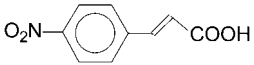
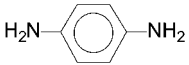
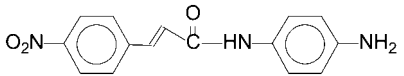
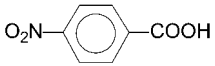
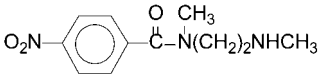
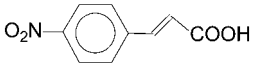
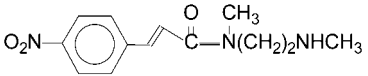
Table 1. Synthesis of acylakylenediamines from carboxylic acids.

Entry	Acid	Diamine	Product	Time (min)	Yield[a,b] (%)	Reference
a	$CH_3(CH_2)_2COOH$			25	89	[15]
b	$CH_3(CH_2)_8COOH$			35	90	[15]
c				30	97	[15]
d				30	93	[15]
e				35	95	[15]
f				40	95	[16]
g				40	89	[16]

h				40	89	[16]
i				45	91	[16]
j				50	89	[16]
k				30	96	
l				25	89	[16]
m				35	86	[17]
n				35	89	[17]

(*continued*)

Table 1. Continued.

Entry	Acid	Diamine	Product	Time (min)	Yield[a,b] (%)	Reference
o				50	82	[17]
p		$H_2N-(CH_2)_2NH_2$		50	85	[15,16]
q		$H_2N-(CH_2)_2NH_2$		30	88	[15,16]
r				40	89	[15,16]
s				35	92	[15,16]
t		$CH_3HN-(CH_2)_2NHCH_3$		50	77	[15,16]
u		$CH_3HN-(CH_2)_2NHCH_3$		55	81	[15,16]

[a]Yields of pure isolated products.
[b]Products were characterized by IR, ^{1}H NMR, elemental analysis, and by comparison with authentic samples.

the completion of reaction (TLC), the solvent was removed, the residue was extracted with *n*-hexane (3 × 5 mL) and washed with water (10 mL) and aq. sodium bicarbonate (10%, 10 mL).The crude product was further purified by column chromatography (pet.ether : ethyl acetate = 8 : 2).

***N*-(2,3-Dihydrobenzo[1,4]dioxin-2-carbonyl)piperazine (6k)**. M.p. = 84–85°C; IR (KBr): 1640, 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 1H, NH), 2.80–2.90 (m, 2H), 2.95–3.00 (m, 2H), 3.50–3.65 (m, 2H), 3.70–3.80 (m, 2H), 4.40 (dd, J = 12.0, 8.5 Hz, 1H), 4.50 (dd, J = 12.0, 2.5 Hz, 1H), 4.90 (dd, J = 8.5, 2.5 Hz, 1H), 6.90–7.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.2 (2C), 45.7, 50.3, 65.1, 70.5, 115.1, 120.2, 122.4, 123.9, 144.2, 145.6, 170.2; EIMS : m/z (%) = 248 (M^+, 25), 111 (100); Anal. calcd. for $C_{13}H_{16},N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.02; H, 6.41; N, 11.35.

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