Pergamon

Tetrahedron Letters 39 (1998) 71–74

TETRAHEDRON LETTERS

2-(2-Aminophenyl)-acetaldehyde Dimethyl Acetal: A Novel Reagent for the Protection of Carboxylic Acids.

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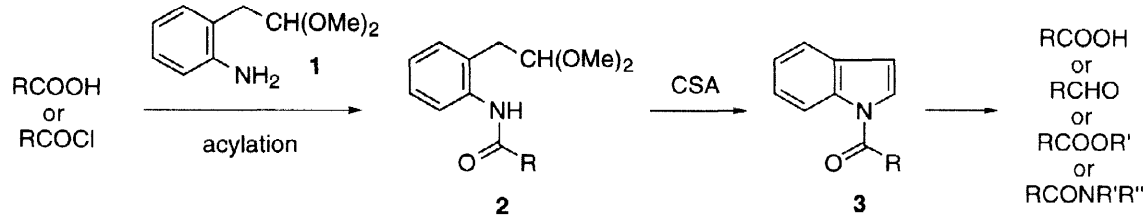
Received 29 September 1997; revised 23 October 1997; accepted 24 October 1997

Abstract: The synthesis and use of 2-(2-aminophenyl)-acetaldehyde dimethyl acetal **1** are described. The amides **2**, derived from this amine and carboxylic acids, are stable under basic conditions and thus can be regarded as the protected carboxylic acids. The corresponding carboxylic acids are regenerated by conversion of **2** into indolylamides **3** by treatment with CSA and subsequent hydrolysis with LiOOH or NaOH. In addition, **3** can be easily converted to esters, amides, and aldehydes.

Although numerous protecting groups for carboxylic acid have been devised to date, none appears to be stable under strong basic conditions and yet can be deprotected under mild conditions.[1] Ortho esters and amides are generally used as base-stable protective groups. A major drawback of the former is that they are difficult to prepare directly from carboxylic acids. On the other hand, removal of the amide-based protective groups usually requires forcing conditions and therefore may lack general applicability. We report herein that the novel amides **2**, which can be prepared from the parent acids and 2-(2-aminophenyl)-acetaldehyde dimethyl acetal (**1**), are stable under basic conditions and can be easily deprotected via the corresponding indolylamides **3** under mild conditions.[2] In addition, we have demonstrated that the indolylamides **3** can be converted into other carbonyl compounds including esters, amides and aldehydes in high yields.

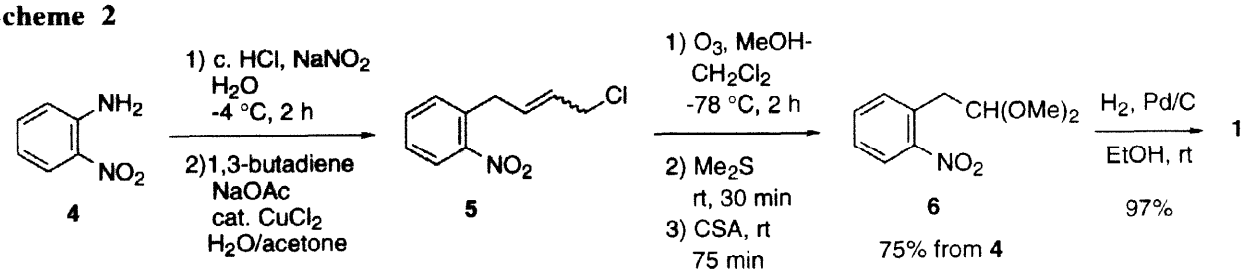
Scheme 1



Compound **1** was prepared in a simple 4-step sequence starting from 2-nitroaniline (**4**) (Scheme 2). Treatment of the diazonium salt derived from 2-nitroaniline (**4**) with butadiene[3] in the presence of $CuCl_2$ afforded 1-(2-nitrophenyl)-4-chloro-2-butene (**5**). The crude product thus obtained was subjected to ozonolysis in MeOH, followed by dimethyl acetal formation to give 2-(2-nitrophenyl)-acetaldehyde dimethyl acetal (**6**). Finally, reduction of the nitro group over palladium on carbon afforded compound **1** in 73% overall yield from **4**.[4]

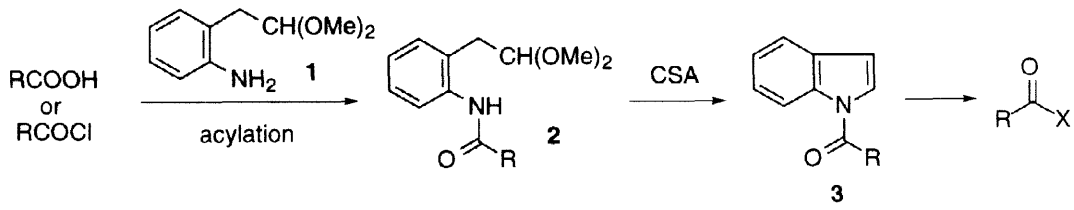
0040-4039/98/$19.00
PII: S0040-4039(97)10491-9

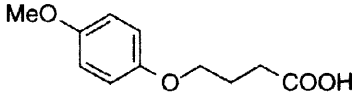
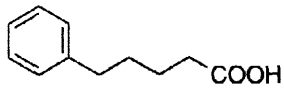
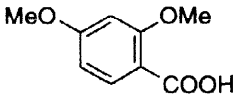
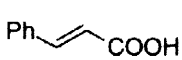
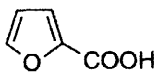
Scheme 2



The amide formation of alkyl, aryl and α,β-unsaturated carboxylic acids or acid chlorides with compound **1** underwent smoothly by treatment with DCC and catalytic amount of DMAP or in pyridine, respectively (Table 1). These amides **2** can withstand such basic conditions as 3N NaOH (in MeOH at rt for 2 h) and $LiBH_4$ (in THF at rt overnight). For deprotection, the amides **2** were first converted to the corresponding indolylamides **3** with acid catalysts as illustrated in Table 1. The parent carboxylic acids were regenerated either by conditions A (LiOH, H_2O_2) or conditions B (3N NaOH in MeOH) in nearly quantitative

Table 1. Protection, Deprotection and Conversion to Ester or Amide.[a]



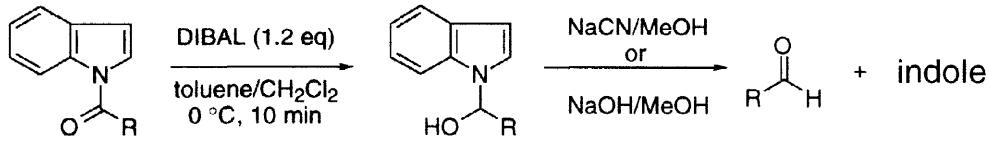
carboxylic acid	amide % yield	indolylamide % yield time		% yield	conditions[g]	time (h)
	88[b]	79[d] 2 h	X = OH	90 100	A B	2 3.3
			X = OMe	100	C	1.4
	—	93[e]	X = NH-n-Bu	90	D	10
			X = 	98	E	3
	84[c]	82[f] 2 h	X = OH	87 84	A B	3 days 35
	86[c]	93[f] 40 min	X = OH	75 97	A B	6 3.4
			X = OMe	90	C	1
	77[c]	84[f] 5 h	X = OH	87 99	A B	2.5 2.5
			X = OMe	83	C	2.5

[a]All yields based on isolated products. [b]RCOOH, DCC (1.5 eq), DMAP (0.1 eq), CH_2Cl_2, rt, 1h. [c]RCOCl, pyridine, rt, 1 h. [d]CSA (0.05 eq), quinoline (0.1 eq), benzene, reflux. [e]Indolylamide was obtained without isolation of amide. [f]PPTS (0.05 eq), benzene, reflux. [g]A: LiOH, H_2O_2, THF/H_2O. B: 3N NaOH, MeOH. C: Et_3N (0.1 eq), MeOH. D: excess n-$BuNH_2$, cat. DMAP, toluene, reflux. E: excess pyrrolidine, cat. DMAP, toluene, reflux.

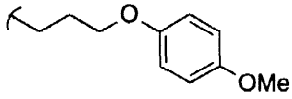
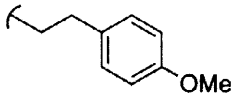
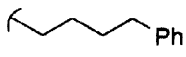
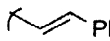
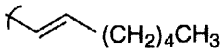
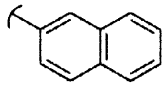
yields. Being susceptible to nucleophilic attacks, the indolylamides **3** can also be converted to esters and other amides by treatment with appropriate nucleophiles.

In connection with our other project, indolylamides **3** were subjected to DIBAL reduction. Surprisingly, the corresponding hemiaminals **7** could be isolated in good to excellent yields when the reaction was terminated by addition of acetic acid (Table 2). The overreduced primary alcohols, which might arise from the reduction of the liberated aldehydes **8**, could not be detected at all. These phenomena were observed not only for the substrates bearing oxygen functionality in the molecule, but also for the simple alkyl substrates, excluding the possibility of intramolecular chelation to stabilize the aluminum alcoholate intermediate.[5] Generation of the aldehydes **8** from **7** could be achieved under very mild conditions. Thus, treatment of hemiaminals **7** with 0.15 equivalent of NaCN in MeOH at reflux conditions afforded aldehydes **8** in high yields without forming aldol products. In the case of aryl and α,β-unsaturated amides, aldehydes **8** were obtained by partitioning the crude products of the DIBAL reduction between 1N NaOH and ethyl acetate or by stirring in 1N NaOH/MeOH without isolation of the corresponding hemiaminals.

Table 2. Conversion of Indolylamide to Aldehyde.[a]



3 **7** **8**

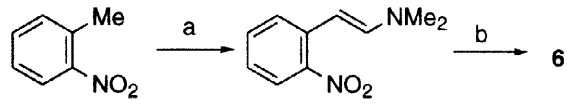
R	hemiaminal	aldehyde
	86	79[b]
	99	77[b]
	90	81[b]
	—	85[c]
	—	62[d]
	—	83[e]

[a]Yields based on isolated products. [b]NaCN (0.15 eq), MeOH, 60 °C, 1 h. [c]$NaBH_4$ (2 eq), $CeCl_3$, $MeOH/CH_2Cl_2$, -20 °C, 25 min. [d]Partitioned between 1N NaOH and EtOAc. [e]1N NaOH, MeOH, rt.

In summary we have demonstrated that 2-(2-aminophenyl)-acetaldehyde dimethyl acetal is readily available and can be used for protection of carboxylic acids. The amides prepared from this amine and carboxylic acids or acid chlorides not only serve as base-stable protected carboxylic acids, but also can be converted to esters, amides, and aldehydes. The regeneration of carboxylic acid was carried out in a mild 2-step procedure via indolylamide.

References and Notes

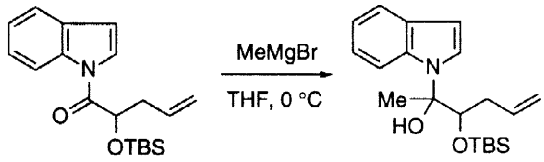
1. For general references on protective groups, see: Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis;* John Wiley and Sons: New York, 1991.
2. For protection of carboxylic acid as N-acyl indoline and deprotection via indolylamide, see: de Oliveira Baptista, M. J. V.; Barrett, A. G. M.; Barton, D. H. R.; Girijavallabhan, M.; Jennings, R. C.; Kelly, J.; Papadimitriou, V. J.; Turner, J. V.; Usher, N. A. *J. Chem. Soc., Perkin Trans 1* **1977**, 1477. Barrett reported that ozonolysis of amide derivative of 2-allylaniline and subsequent acid treatment led to indolylamide, which can be converted to indole and carboxylic acid. Barrett, A. G. M.; Dhanak, D. *Tetrahedron Lett.* **1987**, *28*, 3327.
3. (a) Noland, W. E.; Sellstedt, J. H. *J. Org. Chem.* **1966**, *31*, 345. (b) Acheson, R. M.; Hunt, P. G.; Littlewood, D. M.; Murrer, B. A.; Rosenberg, H. E. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1117.
4. Alternatively, compound **1** could be prepared from 2-nitrotoluene utilizing Leimgruber-Batcho enamine synthesis, subsequent dimethyl acetal formation under acidic conditions, and reduction of the nitro group. Batcho, A. D.; Leimgruber, W. *Org. Synth. Coll. Vol. VII***1990**, 34.



(a) $Me_2NCH(OMe)_2$, DMF, reflux overnight. (b) CSA (3 eq), MeOH, reflux, 9 h, 74% (2 steps).

^1H NMR data of 2-(2-aminophenyl)-acetaldehyde dimethyl acetal (**1**): (400 MHz, $CDCl_3$) δ 2.87 (d, J = 5.4 Hz, 2 H), 3.38 (s, 6 H), 4.05 (br s, 2 H), 4.50 (t, J = 5.4 Hz, 1 H), 6.68 (dd, J = 1.0, 8.0 Hz, 1 H), 6.74 (ddd, J = 1.0, 7.4, 7.4 Hz, 1 H), 7.06-7.07 (m, 2 H).

5. Attempts to prepare ketones via indolylamide were unsuccessful. Thus, addition of methyl lithium to indolylamides afforded a ca. 4:1 mixture of methyl ketones and tertiary alcohols. In the case of α-hydroxyl compound **9**, however, addition of methyl magnesium bromide led to a clean formation of the isolable hemianinal **10** as a single isomer.



9 **10**