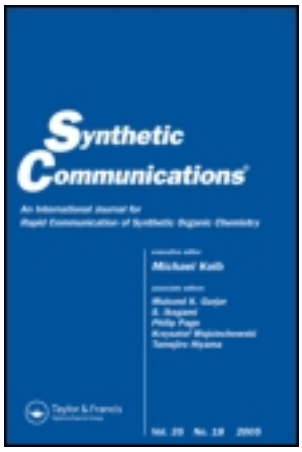

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Manas Chakrabarty [a] , Nandita Ghosh [a] , Shampa Khasnobis [b] & Manju Chakrabarty [c]
[a] Department of Chemistry, Bose Institute, 93/1, A.P.C. Road, Calcutta, 700 009, India
[b] Department of Chemistry, Acharya J.C. Bose College, Calcutta, 700 020, India
[c] Department of Chemistry, Bethune College, Calcutta, 700 006, India
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DBU, A HIGHLY EFFICIENT REAGENT FOR THE FACILE REGENERATION OF (HETERO)ARYLAMINES FROM THEIR ACETAMIDES AND BENZAMIDES: INFLUENCE OF SOLVENT, TEMPERATURE, AND MICROWAVE IRRADIATION

Manas Chakrabarty,[1,*] Nandita Ghosh,[1] Shampa Khasnobis,[2] and Manju Chakrabarty[3]

[1]Department of Chemistry, Bose Institute, 93/1, A.P.C. Road, Calcutta 700 009, India
[2]Department of Chemistry, Acharya J.C. Bose College, Calcutta 700 020, India
[3]Department of Chemistry, Bethune College, Calcutta 700 006, India

ABSTRACT

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was found to smoothly cleave the *N*-acetyl and *N*-benzoyl derivatives of carbazoles, indoles and nitroanilines quickly in refluxing methanol and the parent amines were recovered in excellent yields. Complete cleavage could also be accomplished in acetonitrile solution under reflux and also under microwave

*Corresponding author. E-mail: manas@boseinst.ac.in

irradiation, which, however, required considerably longer periods.

The cleavage of amides to amines, a common step in many organic syntheses, is usually carried out by treatment with mineral acid or caustic alkali, often requiring prolonged periods of heating.[1–4] Several other reagents have also been reported for special cases, e.g. heating with hydrazine hydrate in case of *N*-acetylglucosaminides,[5] electrolysis of benzamides in presence of tetramethylammonium chloride,[6] Meerwein's reagent for acetamidodeoxysugars,[7] DIBAL for the reductive debenzoylation during a synthesis of quinine and quinidine,[8] polyhydrogen fluoride for *N*-debenzoylation of cytosines and adenines,[9] fusion with phenol for *N*-debenzoylation during peptide synthesis,[10] etc. But harsh reaction conditions (e.g. sealed tube, 100°), long reaction time (e.g. 20 h), wide ranging yields (8–99%) and lack of generality are the principal limitations of these methods. Consequently and even otherwise, there is always a need for the development of new, milder reagents which would not require the use of particularly any acid or alkali.

While trying to develop a new synthesis of pyrrolocarbazoles, a recently reviewed class of bioactive heterocycles,[11] employing the Barton-Zard pyrrole synthesis,[12] *N*-acetyl-3-nitrocarbazole (**1a**) was treated with ethyl isocyanoacetate (EIA) in presence of DBU in tetrahydrofuran for 20 h. The sole product, isolated in quantitative yield, was identified as 3-nitrocarbazole. It was a clear case of *N*-deacetylation, in which EIA was not likely to have played any role. The reaction was, therefore, repeated without EIA, when 3-nitrocarbazole was again isolated as the only product in quantitative yield in 7 h. These results suggested that DBU was responsible for the observed *N*-deacetylation, which prompted us to check the generality of this property of DBU on a few carbazoles and indoles.

Since the reaction of **1a** in tetrahydrofuran at room temperature still required rather long time (7 h) for completion, it was repeated using acetonitrile and methanol separately at room temperature and under reflux. The cleavages were found to be equally slow at room temperature in all three solvents and practically independent of the stoichiometry of DBU used. But the reactions were quite fast in refluxing tetrahydrofuran and acetonitrile and much faster in refluxing methanol, being directly related to the concentration of DBU. *N*-Acetylcarbazole (**1b**), for example, required 3, 2.5 and 2 h, respectively for complete *N*-deacetylation using 1, 2 and 5 equivalents of DBU. In all subsequent experiments, two equivalents of DBU were, therefore, used as a compromise amount.

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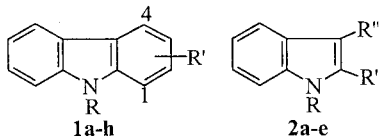
The necessary conditions having been established, the reagent was tried with carbazoles (**1a–1f**) and indoles (**2a–2d**) in both acetonitrile and methanol using two equivalents of DBU. The results (Table 1) showed that all but one substrate, viz. *N*-acetyl-1-nitrocarbazole (**1e**) underwent facile cleavage, from which the amines were recovered in excellent yields following simple aqueous or non-aqueous work-ups, developed by us. The failure observed in the case of **1e** was most likely the result of steric crowding around the carbonyl carbon.

The reagent was next applied on acetanilide (**3a**), *N*-methylacetanilide (**3b**), *N*-acetyldiphenylamine (**3c**) and benzanilide (**3d**) under similar conditions. Unexpectedly, the reagent proved abortive in all the cases. In

Table 1. Cleavage of Amides to Amines by DBU*



Amide (ref.)	R	R'	R"	Reaction Time (hr) in MeOH	Reaction Time (hr) in CH_3CN	Yield (%) of Amine
1a (13)	Ac	H	-	0.5	2.5	99
1b≠	Ac	3-Me	-	0.5	2.5	97
1c≠	Ac	2-Me	-	0.5	2.5	96
1d (14)	Ac	3-NO_2	-	1.0	1.5	96
1e (14)	Ac	1-NO_2	-	F	F	-
1f (15a)	COPh	H	-	0.5	2.0	97
1g (16)	SO_3Ph	H	-	F	F	-
1h (17)	Tosyl	3-NO_2	-	1.0	1.5	96
2a (15b)	Ac	H	H	0.5	3.5	98
2b (15c)	Ac	H	Me	0.5	4.0	97
2c (15d)	Ac	Me	Me	0.5	4.5	96
2d (15h)	COPh	H	H	0.5	2.5	96
2e (18)	Tosyl	H	H	F	F	-

*0.3 mM of amide and 2 equivalents of DBU were used throughout. The regenerated amines were identified by comparison (m.p., m.m.p. and co-tlc).
≠Identified by elemental analysis, IR and MS. F stands for failure even after 8 hr of refluxing.

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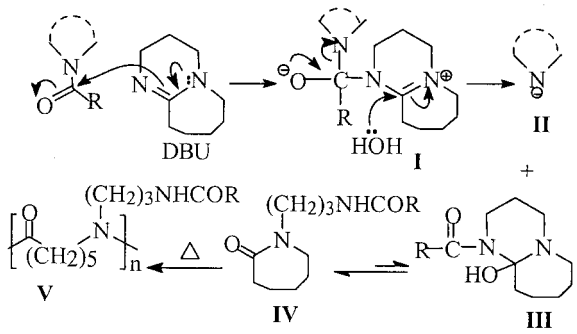
order to trace the reason for this failure, the mechanism of the cleavage of amides (Scheme 1) had to be looked into.



Scheme 1. Mechanism of DBU-mediated cleavage of *N*-acetyl/benzoyl(hetero)-arylamines.

The cleavage of amides is known to be an acyl transfer reaction initiated by the nucleophilic attack of DBU at the amide carbonyl, leading to the tetrahedral intermediate **I**. The cleavage of C–N bond then takes place concurrently with an attack by a water molecule at the imminium carbon, leading to the amine anion **II** and the amino alcohol **III**. Since the cleavage of the C–N bond of **I** depends upon its stability as well as upon the stability of the resulting anion **II** (the leaving group), we envisaged that the introduction of a group with both −I and −M effects (e.g. nitro group) at *ortho*- or *para*-positions of the ring would impart the desired stability. Indeed, the *N*-acetyl and *N*-benzoylnitroanilines (**3e–3i**) were cleaved nearly quantitatively by two equivalents of DBU in refluxing acetonitrile, or better, in refluxing methanol, in comparable time spans (Table 2).

The reagent, however, proved ineffective for *N*-benzenesulphonylcarbazole (**1g**) and *N*-tosylindole (**2e**), but it successfully cleaved 3-nitro-*N*-tosylcarbazole (**1h**). Since eco-friendly reactions are the need of the day, irradiation with microwaves, instead of refluxing, in acetonitrile solution containing two equivalents of DBU was also tried on a few representative amides (**1a, 1d, 1f, 2b, 2d, 3e**). Except for *N*-acetyl-3-nitrocarbazole (**1d**), the reagent brought about the cleavages quantitatively but required more time than in refluxing methanol. We ae unable to offer any befitting explanation for the failure of *N*-acetyl-3-nitrocarbazole (**1d**) to undergo cleavage under microwave irradiation although the same takes place easily under thermal conditions.

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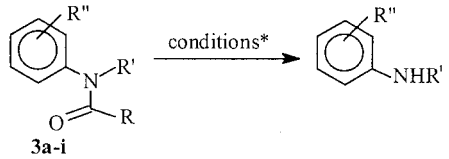
Table 2. Cleavage of Amides to Amines by DBU*



3a-i

Amide (ref.)	R	R'	R''	Reaction Time (hr) in MeOH	Reaction Time (hr) in CH_3CN	Yield (%) of Amines
3e (15e)	Me	H	2-NO_2	0.5	4.5	95
3f (15e)	Me	H	4-NO_2	1	5.5	96
3g (15e)	Ph	H	2-NO_2	1	4.5	95
3h (15f)	Ph	H	4-NO_2	1.5	5	97
3i≠	Me	Ph	2-NO_2	3.5	7.5	96

*All conditions as in Table 1. ≠Identified by elemental analysis, IR and MS.

Table 3. Results of Amide Cleavage Under Microwave Irradiation*

Amide (0.3 mM)	**1a**	**1d**	**1f**	**2b**	**2d**	**3e**
Reaction time (h)	1.5	F	0.8	2.25	2	2.5

*Carried out in acetonitrile solution. F stands for failure even after 4 h of irradiation.

An important outcome of our experiments is that it provides yet another evidence in support of the nucleophilicity of DBU which is widely documented in the literature as a non-nucleophilic base.[19,20] Along with others, we too have earlier proved this nucleophilic property of DBU.[21,22] Regarding the fate of DBU, the ring opening of the amino alcohol **III** is expected to lead to the caprolactam derivative **IV**. Paralleling the formation of 'nylon 6' by the heating of caprolactam itself,[23] **IV** can be expected to polymerise under reflux to **V** which could not be isolated by any of the procedures adopted by us.

To summarise, we have developed a mild and extremely facile method,[24] which does not require the use of acid or alkali, for the regeneration of (hetero)aryl-amines from their *N*-acetyl and *N*-benzoyl derivatives where the amide carbonyls have at least moderately strong carbocation character. Besides, the isolation procedures are simple, the yields are consistently excellent and microwave irradiation can be used as an effective

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alternative to heat. We hope that the method would be of use to the community of chemists.

EXPERIMENTAL

Melting points were recorded on a Toshniwal melting point apparatus and are uncorrected. The IR spectra were recorded on a Nicolet 410 FT-IR spectrophotometer and the mass spectra (LREIMS) on a Kratos AEI MS1 mass spectrometer. Column chromatographies were performed over silica gel (60–120 mesh; Qualigens, India) and TLC on silica gel G (E. Merck, India) plates. DBU was purchased from Aldrich, USA. Petrol refers to petroleum ether, b.p. 60–80°. All amides except **1b**, **1c** and **3i** and the heteroarenes 2- and 3-methylcarbazoles[25] and 1- and 3-nitrocarbazoles[14] were prepared by literature procedures. The amides **1b** and **1c** were prepared by acetylation (Ac_2O, $BF_3{\cdot}Et_2O$)[13] of the respective carbazoles, and **3i** was prepared by the Goldeberg coupling (K_2CO_3, Cu_2I_2) of 2-nitroacetanilide with bromobenzene, all three having been identified by elemental analysis, IR and MS data, detailed below. All other amines were procured commercially. The regenerated amines were identified by usual comparison (m.p., m.m.p. and co-TLC) with authentic samples.

1b: Colourless flakes, m.p. 72–74° (petrol). Found: C, 80.69; H, 5.85; N, 6.30; calc. for $C_{15}H_{13}NO$: C, 80.72; H, 5.83; N, 6.28%; IR (nujol): 1699 cm^{-1}; EIMS: *m/z* 223 (M^+), 181 (100%).

1c: Colourless flakes, m.p. 88–90° (petrol-$CHCl_3$). Found: C, 80.75; H, 5.85; N, 6.25; calc. for $C_{15}H_{13}NO$: C, 80.72; H, 5.83; N, 6.28%; IR (nujol): 1699 cm^{-1}; EIMS: *m/z* 223 (M^+), 181 (100%).

3i: Yellow granules, m.p. 128–130° (petrol-EtOAc). Found: C, 65.62; H, 4.69; N, 10.94; calc. for $C_{14}H_{12}N_2O_3$: C, 65.64; H, 4.66; N, 10.95%; IR (nujol): 1674 cm^{-1}; EIMS: *m/z* 256 (M^+), 214 (100%).

General Procedure for Cleavage

Thermal: The amide (0.3 mM) in acetonitrile or methanol (10 ml) containing DBU (0.1 ml; 0.6 mM) was refluxed until the amide was consumed (TLC). In the aqueous work-up, the solution was simply poured into water, the precipitated amine filtered under suction and crystallised. In the non-aqueous work-up, the solvent was distilled off and the residue was passed through a silica gel column, when the amine eluted out in 0–10% ethyl acetate in petrol.

Microwave: A solution of the amide (0.3 mM) in acetonitrile (10 ml) containing DBU (0.1 ml; 0.6 mM) was irradiated with microwave using a BPL-SANYO domestic microwave oven (800 W; 2450 MHz), operating at 30% power and being discontinued after every 3 min, till the completion of the reaction (TLC). The reaction mixture was then taken out, cooled to room temperature and worked up as before.

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