Solid-phase Synthesis of Tertiary *N*-Methyl Amines Including Tropanes

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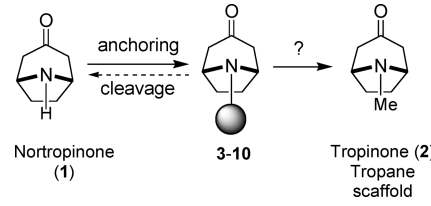
Synthesis on solid phase is one of modern methodologies especially useful in parallel and combinatorial syntheses.[1] Tertiary amine functionalities are found in many important classes of catalysts, reagents and biologically active compounds. The tertiary *N*-methyl group is also present in structures of tropane alkaloids[2,3] and majority of synthetic tropane derivatives with potential biological activity.[4] Despite of well-defined tropane scaffold structure, which is present in known or potentially bioactive functionalized tropane derivatives[5] only a few approaches to tropanes libraries[6−9] and supported synthesis[10−12] have been studied. Our approach to supported synthesis of tropane derivatives is based on anchoring nortropinone (**1**, Scheme 1),[13,14] a secondary amine which naturally required a postcleavage N-methylation with one of the known procedures.[15] Although secondary amines can be anchored reversibly via several well-known linkers including activated Wang carbonate,[16,17] and triazene T2,[18,19] we also looked for other methods. The linkers preserving the amine character of the anchored nitrogen atom, such as REM (via Michael addition-Hofmann elimination),[20,21] amino acetals (DSEM and POEM),[22,23] BAL-type,[24,25] BOBA[26] and several widely available polymeric gels (Merrifield,[27−29] trityl chloride[30]), could offer certain advantages. The motivation for seeking such anchors was an observation that the reactions of lithium enolates of tropinone and *N*-benzylnortropinone (both tertiary amines) in solution were more stereoselective and higher yielding than reactions of corresponding N-diazaphenyl (triazene) or carbobenzyloxy (uretane) derivatives.[31] Therefore, we undertook a study on anchoring, and cleavage of nortopinone (**1**) on various polymeric supports with emphasis on methods for conversion of immobilized nortropane scaffold to tertiary amines such as tropane (**2**, Scheme 1).

Solid-phase methods for synthesis of tertiary amines including *N*-methyl amines have been reported by Andersson.[32] Others[20,33−35] reported solid-phase alkylation and cleavage of tertiary amines by Hofmann type elimination from REM-type resins. An interesting method for debenzylating cleavage of quaternized amines from the Merrifield support based on nucleophilic displacement was reported by Cai.[36] In our report, we wish to describe a novel method for preparation of N-methylated tertiary amines, including tropanes, based on quaternization and nucleophilic debenzylation of so formed ammonium salts immobilized via benzyl amine linkage on a widely available solid support, the Wang gel. We also report results of our approaches to reversible immobilization of nortropinone on polystyrene type supports with MOM analogue, BOM analogue, Wang type, PAL-type, Merrifield, *para*-C_3-T2 triazene, carbamate Wang, and trityl linkers (Figure 1).

Reversible Anchoring of the Amino Ketone. The cyclic secondary amines like nortropinone (**1**) could, in principle, be immobilized in a form of a tertiary amine via several linkers such as REM, Wang, and BAL linkers. The REM linker could not be used for our purposes because of its incompatibility with the basic conditions of enolate reactions, such as the directed aldol reaction. The Wang and BAL type linkers are typically used for releasing amine derivatives, usually amides or sulfonamides.[37] However, the recent reports[24,25,38] prompted us to investigate their use for immobilization of amino ketones such as nortropinone. We found that even though nortropinone could be anchored to Wang polymer (to give **6**) and the 2,6-dimethoxy Wang polymer (to give **10**, PAL type linker)[39] very effectively (87−100%, Table 1, Figure 1), cleavage of this amino ketone was not feasible. Attempted oxidative cleavage of the Wang linker **6** (with DDQ[26]) and simple benzylamine linker **7** derived from Merrifield polymer (with ceric(IV) ammonium nitrate, CAN[27]), in our hands, did not provide any amine products (Figure 1). Therefore, we investigated amino acetal linkers analogous to MOM and BOM protecting groups[40] for amines (**8** and **9**, Figure 1). Preparation of similar linkers by two different methods was reported.[22,23] Unfortunately, we were able to obtain only modest loadings of the test amine, 4-benzylpiperidine or nortropinone **1**, via such linkers prepared by either method (Figure 1). The cleavage provided poor loadings of released amines (17 and 9%, Table 1) despite using trifluoroacetic acid (TFA) at different concentrations, addition of water, prolonged cleavage times, and ultrasound. The only practical method for reversible linking of the amino ketone **1** to polymers in the form of a tertiary amine was the reactions with Merrifield gel or trityl chloride gel to form loaded polymers **7** and **3**, respectively (Figure 1). The amino ketone could however be cleaved off the Merrifield support only by the procedure of Leysen et al.[28] (action of 1-chloroethyl chloroformate (ACE-Cl) in 1,2-dichloropropane (DCP), followed by methanolysis) in an analogy to the known reactions in solution,[41−44] albeit with moderate yield (37% of the theoretical loading). As expected, nortropinone was very efficiently anchored and cleaved from supports with trityl linker[45] **3** and carbamate Wang linker[46] **4**, (ca. 100% of the theoretical loadings). Immobilization and

Scheme 1



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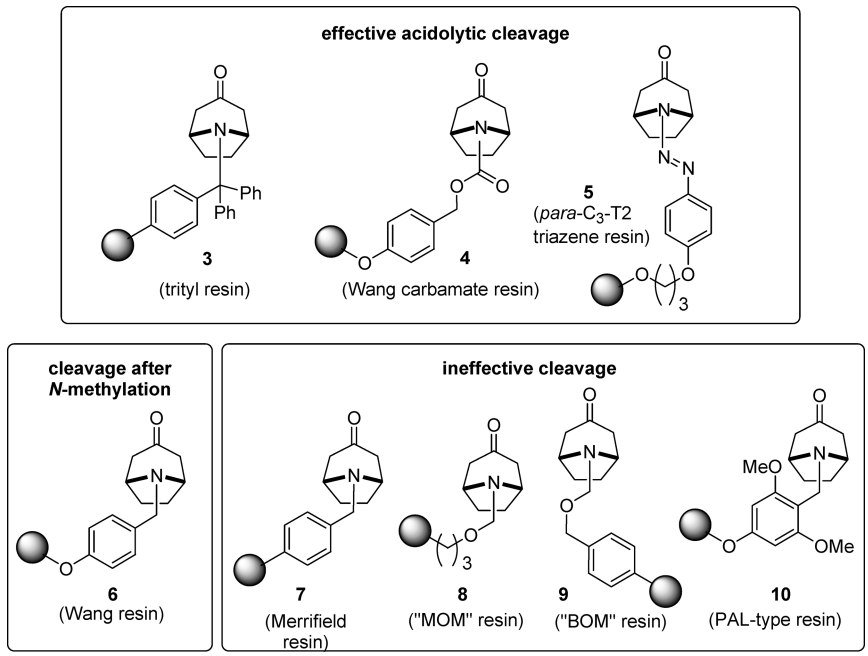


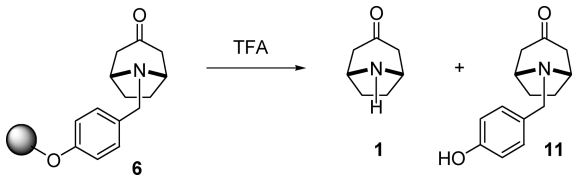
Figure 1

Table 1. Loadings of Nortropinone on Tested Polymeric Supports

			loading of immobilized nortropinone [mmol/g] (%)[a]	
resin	anchoring	cleavage	based on $Et_3N \cdot HCl$[b]	based on nortropinone[c]
3	trityl chloride resin, **1**, DMF, 80 °C	20% TFA/DCM	*d*	1.55 (100)
4	(i) Wang resin, 4-NO_2PhO(CO)Cl, Py, DCM, rt, (ii) **1**, DCM, rt	20% TFA/DCM	*d*	0.87 (100)
5	(i) triazene resin, 10% TFA, −10 °C, (ii) **1**, DCM, −10 °C, (iii) **1**, DCM, rt	10% TFA/DCM	*d*	0.71 (78)
6	Wang resin, $SOCl_2$, DCM, rt	50% TFA/DCM	0.79 (87)	0.79 (87)[e]
7	Merrifield resin, **1**, DMF, 80 °C	i) ACE-Cl/ DCP, ii) MeOH	1.07 (99)	0.40 (37)
8	(i) hydroxybutyl resin; $(HCHO)_n$, HCl, DME, 0 °C (or (1) *t*-BuOK, $ClCH_2SMe$, THF; (2) SO_2Cl_2), (ii) **1**, DME	50−95% TFA/DCM	1.0 (44)	0.39 (17)
9	(i) Wang resin; $(HCHO)_n$, HCl, DME, 0 °C (or (1) *t*-BuOK, $ClCH_2SMe$, THF; (2) SO_2Cl_2), (ii) **1**, DME	50−95% TFA/DCM	0.40 (35)	0.10 (9)
10	$NaBH_3CN$, **1**·HCl, AcOH, EtOH	50−90% TFA/DCM	1.06 (100)	0

[a] % of theoretical value. [b] Loading determined from mass of triethylamine·HCl obtained after washing of the gel with HCl solution followed by washing with triethylamine.[47] [c] Loading determined from mass of nortropinone·HCl obtained after cleavage and conversion to hydrochloride. [d] Method not suitable for determination of loading of bound amines. [e] When accounted for released linker bound to nortropinone after "bind and release" process (Scheme 2).

Scheme 2

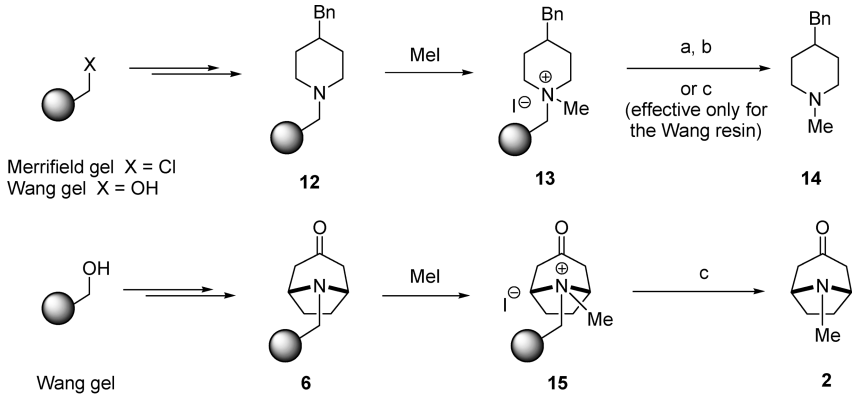


cleavage of the amino ketone under previously optimized conditions[13] from the *para*-C_3-T2 triazene support **5** (the optimal triazene linker for the aldol reaction[14]) was slightly less efficient (61% of the theoretical loading).

To allow for application of highly reactive and basic conditions of enolate chemistry, which have been successfully used for synthesis of various tropane derivatives in solution,[48−50] to reactions of immobilized nortropinone the linker should be sufficiently robust. Although our initial studies[14,51] showed that triazene T2,[14,18] and Wang carbamate[46] anchored nortropinone could be used in supported synthesis based on enolate chemistry the cleaved nortropanes needed additional post cleavage *N*-methylation. Thus we turned our attention to the Wang resin that has been used for binding amines and releasing them after modification as sulfonamides[37] or even primary amines.[38] Unfortunately, our attempts to release unchanged secondary amines especially nortropane derivatives were only partially successful and complicated by byproduct of linker cleavage (Scheme 2). Cleavage of nortropinone and even a simple test amine, morpholine, from the Wang polymer with TFA resulted in a mixture of cleaved amine e.g., **1** and its *N*-(*para*-hydroxybenzyl) derivative **11** in ∼1:1 ratio (Scheme 2, Table 1, resin **6**).[51]

To directly obtain the N-methylated tropane derivatives we investigated a possibility of quaternization of supported nortropane followed by cleavage by debenzylation. W reasoned that some known from solution synthesis debenzylations of quaternary ammonium salts such as thermal

Scheme 3



a) PhSNa, MeOH, 60 °C; b) morpholine, 70 °C; c) CH_3COONa/ CH_3COOH, 100 °C

decomposition,[52−55] or better, nucleophilic displacement with amines (e.g., with morpholine),[36] thiophenol,[56,57] triphenylphosphine[58] or sodium acetate in glacial acetic acid,[59] could perhaps be combined with *N*-methylation to get access to *N*-methylated tertiary amines including tropinone or other tropane derivatives. Thus two amines, nortropinone and 4-benzyl piperidine, were effectively anchored on the Merrifield gel and the Wang resin activated by thionyl chloride (Wang resin chloride). The immobilized amines were N-methylated (quaternized) using methyl iodide or methyl triflate. Interestingly, an acidolitic (50% TFA/DCM) cleavage of the quaternized nortropinone from the Wang gel provided tropinone **2** (in ∼80% purity) admixed with products of linker release. As we expected the polymer bound benzylic quaternary salts were susceptible to nucleophilic attack at the benzylic position with concomitant releasing of the tertiary amine as a nucleofuge. Four nucleophiles were tested: triphenylphosphine in THF, sodium thiophenolate in methanol, sodium acetate in acetic acid and neat morpholine. The thiophenolate, sodium acetate and morpholine were quite effective for cleavage of *N*-methylpiperidine **14** but failed except for sodium acetate and the Wang polymer for tropinone **2** (Scheme 3). The reaction with sodium acetate and the Wang support gave no cleavage in other polar solvents like methanol or DMF. The triphenylphosphine and thiophenolate-based cleavages were complicated by excess reagents, phosphine oxidation, and thiophenolate oxidation byproduct.

The sodium acetate method was then checked on other selected secondary and primary amines (Table 2). In the typical procedure the amines were immobilized on the Wang resin activated by thionyl chloride (Wang resin chloride). The resulting polymer supported benzylic amines were methylated with methyl iodide in DCM solution. Cleavage from polymer to free the tertiary amines was effected by heating the resin to 100 °C with 5 equiv of dry sodium acetate in glacial acetic acid (Scheme 3, Table 2).

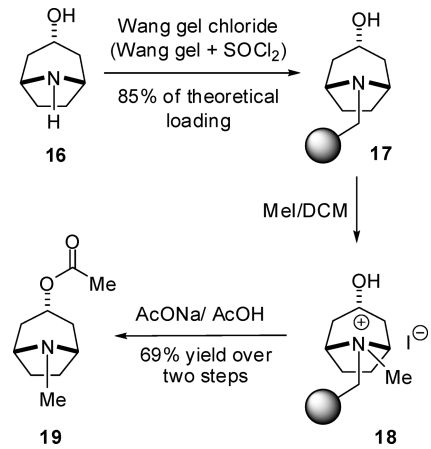
Primary amine, phenethylamine, and benzylamine, gave as major products *N*,*N*-dimethyl derivatives admixed with a few percent of monomethyl derivatives. Unfortunately the method failed for proline benzyl ester and phenylglycine methyl ester. Clearly the harsh condition of cleavage may result in, ester hydrolysis or transesterification. On the other hand, the cleavage conditions could be used for one step

Table 2. Results of Amines Quaternization and Cleavage from the Wang Polymer

amine	theoretical loading of amine [mmol/g]	found loading of amine [mmol/g] (% of theoretical loading)[a]	yield of cleaved N-methylated amine (% of theoretical yield)[b]
dibutylamine	0.90	0.90 (quantitative)	49
phenethylamine	0.91	0.88 (97)	quantitative[c]
piperidine	0.94	0.94 (quantitative)	95
benzylamine	0.92	0.78 (85)	quantitative[c]
4-benzylpiperidine	0.86	0.86 (quantitative)	98
phenylglycine methyl ester	0.87	0.87 (quantitative)	
proline benzyl ester	0.84	0.84 (quantitative)	
nortropinone	0.88	0.88 (quantitative)	quantitative

[a] Loading determined from mass of triethylamine·HCl obtained after washing of the gel with HCl solution followed by washing with triethylamine.[47] [b] Yields based on experimentally found loadings of starting amines, determined from mass of the crude products. Purities ∼90% by ^{1}H NMR and GC-MS. [c] Loading based on a sum of mono and dimethyl derivatives.

Scheme 4



cleavage and hydroxyl acetylation. Accordingly, the method was used to acetylate, a model compound, nortropine **16** (Scheme 4). During cleavage the hydroxyl group of immobilized nortropine underwent effective acetylation giving crude *O*-acetyltropine[60] (**19**, Scheme 4) in quantitative yield (based on nortropine loading) and reasonable purity (>85%). The distillation purified product **19** was obtained in 69% yield. Obviously the stability of ester, hydroxyl, and other functionalities sensitive to the cleavage conditions will be a limitation for wider applicability of the procedure. Nonetheless the procedure may be useful for solid-phase synthesis

of less sensitive *N*-methyl and *N*,*N*-dimethylamines and also for one-step cleavage-acetylation of hydroxy amines.

In summary, we have studied methods for immobilization of nortropinone, a scaffold interesting from the point of view of medicinal chemistry. The amino ketone can be reversibly immobilized on polymeric supports with help of the Merrifield, Wang, Wang carbamate, and triazene linkers. The nortropanes and other secondary or primary amines can be anchored, *N*-methylated and released as *N*-methyl or *N*,*N*-dimethyl amines from supports such as the Wang gel by action of anhydrous sodium acetate in acetic acid. This new two stage quaternization-cleavage procedure could be viewed as an *N*-methylating safety catch method for amines.

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Supporting Information Available. Experimental procedures. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, Germany, 2002; Vol. 1−2.
(2) Lounasmaa, M. In *The Alkaliods*; Brossi, A. , Ed.; Academic Press: New York, 1988; Vol. 33.
(3) Lounasmaa, M.; Tamminen, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 44, p 1−113.
(4) Hoepping, A.; George, C.; Flippen-Anderson, J.; Kozikowski, A. P. *Tetrahedron Lett.* **2000**, *41*, 7427–7432.
(5) Singh, S. *Chem. Rev.* **2000**, *100*, 925–1024.
(6) Angarkov, A.; Gilbertson, S. R. *J. Comb. Chem.* **2008**, *10*, 655–657.
(7) Paparin, J.-L.; Crévisy, C.; Toupet, L.; Grée, R. *Eur. J. Org. Chem.* **2000**, 3909–3918.
(8) Pedersen, H.; Sinning, S.; Bülow, A.; Wiborg, O.; Falborg, L.; Bols, M. *Org. Biomol. Chem.* **2004**, *2*, 2861–2869.
(9) Bulow, A.; Sinning, S.; Wiborg, O.; Bols, M. *J. Comb. Chem.* **2004**, *6*, 509–519.
(10) Koh, J. S.; Ellman, J. A. *J. Org. Chem.* **1996**, *61*, 4494–4495.
(11) Jönsson, D.; Molin, H.; Undén, A. *Tetrahedron Lett.* **1998**, *39*, 1059–1062.
(12) Caix-Haumesser, S.; Hanna, I.; Lallemand, J.-Y.; Peyronel, J.-F. *Tetrahedron Lett.* **2001**, *42*, 3721–3723.
(13) Lazny, R.; Nodzewska, A.; Klosowski, P. *Tetrahedron* **2004**, *60*, 121–130.
(14) Lazny, R.; Nodzewska, A. *Tetrahedron Lett.* **2003**, *44*, 2441–2444.
(15) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696–5700.
(16) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937–941.
(17) Ho, C. Y.; Kukla, M. J. *Tetrahedron Lett.* **1997**, *38*, 2799–2803.
(18) Bräse, S.; Köbberling, J.; Enders, D.; Lazny, R.; Wang, M.; Brandtner, S. *Tetrahedron Lett.* **1999**, *40*, 2105–2108.
(19) Bräse, S.; Dahmen, S.; Pfefferkorn, M. *J. Comb. Chem.* **2000**, *2*, 710–715.
(20) Morphy, J. R.; Rankovic, Z.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3209–3212.
(21) Ouyang, X.; Armstrong, R. W.; Murphy, M. M. *J. Org. Chem.* **1998**, *63*, 1027–1032.
(22) Kim, K.; Wang, B. *Chem. Commun.* **2001**, 2268–2269.
(23) Ruhland, T.; Pedersen, H.; Andersen, K. *Synthesis* **2003**, 2236–2240.
(24) Forns, P.; Sevilla, S.; Erra, M.; Ortega, A.; Fernández, J.-C.; de la Figuera, N.; Fernández-Forner, D.; Albericio, F. *Tetrahedron Lett.* **2003**, *44*, 6907–6910.
(25) Gu, W.; Silverman, R. *Org. Lett.* **2003**, *5*, 415–418.
(26) Kobayashi, S.; Aoki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345–7348.
(27) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *Chem. Commun.* **2000**, 337–338.
(28) Conti, P.; Demont, D.; Cals, J.; Ottenheijm, H. C. J.; Leysen, D. *Tetrahedron Lett.* **1997**, *38*, 2915–2918.
(29) Louërat, F.; Gros, P.; Fort, Y. *Tetrahedron Lett.* **2003**, *44*, 5613–5616.
(30) Jönsson, D.; Erlandsson, M.; Undén, A. *Tetrahedron Lett.* **2001**, *42*, 6953–6956.
(31) Sienkiewicz, M. PhD Thesis, University of Bialystok, Bialystok, Poland, 2008.
(32) Gustafsson, M.; Olsson, R.; Andersson, C.-M. *Tetrahedron Lett.* **2001**, *42*, 133–136.
(33) Plater, M. J.; Murdoch, A. M.; Morphy, J. R.; Rankovic, Z.; Rees, D. C. *J. Comb. Chem.* **2000**, *2*, 508–512.
(34) Brown, A. R. *J. Comb. Chem.* **1999**, *1*, 283–285.
(35) Löber, S.; Gmeiner, P. *Tetrahedron Lett.* **2004**, *60*, 8699–8702.
(36) Cai, J.; Wathey, B. *Tetrahedron Lett.* **2001**, *42*, 1383–1385.
(37) Ngu, K.; Patel, D. V. *Tetrahedron Lett.* **1997**, *38*, 973–976.
(38) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Org. Lett.* **2004**, *6*, 1935–1938.
(39) Boojamra, C. G.; Burow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 5742–5743.
(40) Wuts, P. G. M.; Greene, T. W. *Green's Protective Groups in Organic Synthesis*; 4th ed.; Wiley: Hoboken, NJ, 2007.
(41) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195–196.
(42) Gubert, S.; Braojos, C.; Sacristán, A.; Ortiz, J. A. *Synthesis* **1991**, 318–320.
(43) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081–2082.
(44) Kim, D.-I.; Schweri, M. M.; Deutsch, H. M. *J. Med. Chem.* **2003**, *46*, 1456–1464.
(45) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Org. Lett.* **2003**, *5*, 4183–85.
(46) Raju, B.; Kogan, T. P. *Tetrahedron Lett.* **1997**, *38*, 3373–3376.
(47) Lazny, R.; Michalak, M. *Synlett* **2002**, 1931–1934.
(48) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *60*, 5825–5830.
(49) Majewski, M.; Lazny, R.; Ulaczyk, A. *Can. J. Chem.* **1997**, *75*, 754–761.
(50) Pollini, G. P.; Benetti, S.; De Risi, C.; Zanirato, V. *Chem. Rev.* **2006**, *106*, 2434–2454.
(51) Lazny, R.; Nodzewska, A.; Sienkiewicz, M. *Pol. J. Chem.* **2006**, *80*, 659–661.
(52) Leffek, K. T.; Tsao, F. H.-C. *Can. J. Chem.* **1968**, *46*, 1215–1220.
(53) Burns, J. T.; Leffek, K. T. *Can. J. Chem.* **1969**, *47*, 3725–3728.
(54) Ko, E. C. F.; Leffek, K. T. *Can. J. Chem.* **1970**, *48*, 1865–1868.
(55) Ko, E. C. F.; Leffek, K. T. *Can. J. Chem.* **1971**, *49*, 129–132.
(56) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wagatsuma, N.; Wakisaka, K. *Tetrahedron Lett.* **1969**, *10*, 635–638.
(57) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wagatsuma, N.; Wakisaka, K.; Kusama, O. *J. Med. Chem.* **1969**, *12*, 694–696.
(58) Dekady, L. W.; Korytsky, O. L. *Tetrahedron Lett.* **1979**, *20*, 451–452.
(59) Brasen, W. R.; Hauser, C. R. *Org. Synth., Coll.* **1963**, *4*, 582–584.
(60) Petrović, G. B.; Saičić, R. N. Ěekovićž. M. *Helv. Chem. Acta* **2003**, *86*, 3179–3186.

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